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ESTABLISHING CERTIFICATION AND REGULATION OF THE PRACTICE OF PATHOLOGY*

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History records that the practice of medicine was first regulated and elevated to professional rank by the requirement of standards of competence of physicians in Arabia during the 6th Century. This regulation of medical practice began as a governmental function of protection for the public and has continued thus to the present time.

In its rapid stride since the fundamental discoveries of the 18th Century, modern medicine has accumulated such a vast store of knowledge that the individual physician can only reasonably apply a relatively small portion of the diagnostic or therapeutic methods necessary to practice in general. Under these conditions individual progress can best be made by diligent application in a limited field. Special attainment in such a limited field with its employment by physicians in a consultative capacity constitutes our modern specialty practice. For this reason the determination of competence to do specialty practice should constitute a function of the medical profession in general, or a specialty group in particular.

The tremendous increase in the number of specialties and specialists during the past few years made apparent the necessity of regulation of this type of practice. The first step in this direction was made in 1917 when the American Society of Ophthalmologists established an examining Board to certify competence in their practice. The American Board of Ophthalmology was

*Presidential Address read by Dr. R. A. Kilduffe before the Fifteenth Annual Convention of the American Society of Clinical Pathologists, Kansas City, Missouri, May 8 to 10, 1936.

†Dr. Johns died on April 29, 1936.

followed by the American Board of Obstetrics and Gynecology and the American Board of Dermatology and Syphilology.

Thus prompted, the American Medical Association authorized in 1933 the Council on Medical Education to standardize and coördinate the regulation of medical specialty practice. An Advisory Board for Medical Specialties was organized in 1934 composed of members representing the medical specialty examining boards and such other interested medical groups as the Association of American Medical Colleges, the American Hospital Association, the Federation of State Medical Boards and the National Board of Medical Examiners. Certifying Boards of Pediatrics, Psychiatry and Neurology, Radiology and Urology have since been organized, accepted and admitted to membership representation on this Board.

In his Presidential address to this Society of last year, Dr. Frederick Lamb made very clear the great need for, and desirability of, some plan for the regulation of the practice of clinical pathology. He further pointed out the responsibility of initiating such a project by the group most actively engaged in the practice of this specialty. In conclusion he said: "In these respects, and finally in that of resolute leadership, I have faith that the American Society of Clinical Pathologists will not be found wanting." That this faith was not mistaken, I would make a matter of record.

With the approval by this Society of a plan for the formation of a Certifying Board in Pathology to function in coördination with all other medical specialty certifying Boards under the direction of the American Medical Association, the regulation of the practice of pathology was initiated.

Partly to anticipate the report of our Committee on Certification I will state that the final plans for a Certifying Board of Pathology, to be composed of representatives from the American Society of Clinical Pathology, the Section on Pathology and Physiology of the American Medical Association and the American Society of Pathologists and Bacteriologists, have been completed. With the formal approval of the American Medical Association Advisory Council on Medical Specialties practically assured, legal incorporation and organization of the Board may be confidently expected in the immediate future.

Certification marks the beginning of the regulation of the practice of pathology. By its method of organization with the approval and active support of the leaders of organized medicine it formally proclaims the desire of the medical profession to assume its full measure of responsibility to the public in this regard. This marks an event that should rank in importance to this specialty as did the inauguration of regulation for medical practice in general. In commemoration of the importance of this event to the practice of pathology it is appropriate that we should review all of those measures by which regulation of this specialty may be established and maintained in an effective way.

The Board will be incorporated as a separate legal corporation whose Directors will be composed of nominees from the organizing societies. It will have membership in the group comprising the Advisory Board for Medical Specialties of the American Medical Association. Thus organized and supported it should effectively function to (1) provide and maintain high standards of qualification for the practice of pathology and clinical pathology; (2) provide for the examination of voluntary candidates for certification; (3) issue certificates of competence; (4) issue pertinent information regarding qualified pathologists to the medical profession, medical schools and hospitals; and (5) supervise, or seek the establishment of adequate training facilities to meet the required standards.

To aid in the immediate incorporation and organization of this Board we have a number of most important duties yet before us. An enormous task confronts the membership of this first Board. The evaluation of the varied training and accomplishment of a large group of specialists who have worked under a variety of conditions calls for ability, judgment and energy. The establishment of standards and qualifications of practice requires a high grade of academic training that has been tempered with much application in practice. The initial success of this Board rests upon the extreme care and deliberation with which this selection is made by the contributing specialty societies.

The specialty groups represented by this Certifying Board and the support of the associated groups in the American Medical Association Council on Medical Specialties should insure a general

acceptance of the authority of the Board to qualify pathologists. With the responsibility of having initiated this project the members of this Society are in duty bound to immediately present themselves for examination and certification. While this will undoubtedly involve a considerable sacrifice for many, the importance of united support of certification by our large group of pathologists will lend sufficient weight to the merits of the plan to secure the coöperation of those non-members who may have not yet been impressed with the necessity of this action. A general acceptance of certification by the majority of pathologists who are presently engaged in practice is essential for the stimulation of the group that immediately follows us to extend their study and training to meet the higher average requirements contemplated by the establishment of this qualifying Board.

Higher standards of qualification for the practice of pathology and clinical pathology to be required in 1938 warrants the immediate providing of increased facilities for training. The interest of this Society in promoting certification and the position of a large number of its members in the directorship of hospital and medical college laboratories should enable the anticipation of this need of the Certifying Board to be met. Internships in pathology have been at a premium for some time. In the 1509 hospitals of 100 bed capacity or over that are approved for general intern training by the American Medical Association only seventy-nine offer a total of 125 residencies in pathology. These are almost entirely for a one year service. A goodly number of the men trained in these positions do so as a foundation for other specialties. These must be discounted. We may readily appreciate the fact that the requirement of one year in general pathological training will require at least a doubling of the present number of such internships to meet the normal needs of the specialty.

To cover properly and consecutively the special training requirements in the various branches of clinical pathology and pathologic anatomy will require a reorganization and a total increase of the junior staff positions and fellowships in our large hospital and medical college laboratories. The need for Certification in Pathology has been occasioned to a considerable extent

by a lack of available pathologists to fill all positions offered. The production of an increased number, simultaneously with the elevation of the requirements to practice, is also a matter of concern. Our contacts with medical students and interns must be utilized by design to lead to a greater desire to train in this specialty.

In order to assist the Certifying Board in promoting an increase of special training facilities and students to train, as well as for the purpose of promoting our general interest in the subject,—I would suggest that this Society authorizes the formation of a standing Committee on "Training in Pathology." One of the first duties of this Committee could very well be the promotion of adequate courses in gross and microscopic pathologic anatomy to complete the qualifications for full certification in pathology of a considerable number of clinical pathologists now engaged in practice. Such courses should be developed in our graduate medical colleges where they may be fully standardized and made available to all applicants.

These measures by means of which we may aid in the establishment of certification must not diminish our activity in promoting full regulation for the practice of pathology. Our endorsement and active support of certification has indicated a keen appreciation of the danger of allowing any portion of incompetent practice to reflect discredit upon the practice of pathology or to lessen the value or security of its application. In the delegation of our own legally qualified group of specialists to the regulating influence of a certifying board we have set an example that should enable us to propose and demand the extension of some form of regulation for all medical laboratory work. This refers particularly to the activities of those technical assistants whose right to practice any part of pathology is directly dependent upon the assumption of their legal responsibility by individual physicians. Such technical laboratory work is so intimately linked with medical diagnosis that it cannot be separated from the practice of medicine. Its competent performance and application in practice requires a knowledge not only of the procedures employed but one also capable of evaluating the scope and limitations of their applica-

tion in the diagnosis or treatment of disease. At present a considerable portion of this technical work is performed without supervision or legal medical responsibility. There are no figures available by which we may approximate the extent of this practice. There are only 852 full or part time pathologists and clinical pathologists listed in the directory of the American Medical Association for the entire United States and its territories. This small group can only do or supervise a relatively small quantity of the work in pathology that the present day type of practice requires for the fifteen millions of population embraced in this area. The average ratio of one pathologist to every 175,000 persons is actually larger in some of the sectional groups of the United States proper. Technical work that is competently performed and adequately supervised is a most necessary part of the practice of pathology. The unsupervised practice of an undeniably large group of laboratories can only be considered as a menace to the ideals for which we are striving.

The problem of regulation for the "technical" practice of pathology must be considered from several angles. In a general way the existence of this practice has been due primarily to an insufficient number of pathologists to fill all of the positions of lesser importance, the general medical impression that laboratory work was technical rather than diagnostic and the capitalization of this belief by hospital administrations in owning and operating their own laboratories. Plans for establishing regulation should contemplate changes in all of these basic faults.

We have already initiated a monumental work in the functions of our Registry of Technicians that if utilized to its full extent should satisfy all need for determining the competence of technical assistants. We should be able to increase the number of pathologists to the extent necessary to supervise the laboratories of the great majority of our hospitals and clinics. To require the use of competent technical work under competent supervision, however, will require an altering of the present form or ownership or conduct of a large number of hospital and clinic laboratories.

These institutions must be induced to realize that the practice

of pathology is part and parcel of the practice of medicine. They may properly own the equipment and location of such laboratories, but the right to practice pathology for which this is provided constitutes a medical practice act for which the pathologist alone is morally and legally qualified. We should definitely make some declaration of the most desirable plan of hospital laboratory organization that may be used as a guide for the activities of this Society in promoting these necessary changes. Assistance in effecting these reforms may be obtained through our representation on the Certifying Board of Pathology and its liaison with the American Medical Association Council on Medical Education and Hospitals and the American Hospital Association. The securing of competent supervision for all of the approved hospitals rated by the American Medical Association should be our first goal. At least, supervision of these laboratories would mean regulation of a large part of this practice.

In this review of the measures by which regulation of the practice of pathology may be established and maintained it becomes apparent that whereas we have initiated and accomplished the beginning of this regulation there is yet more to be accomplished before effective control can be maintained. To this end let us individually prove by the support of certification that we are worthy of our responsibility to competently render service in this specialty. Let us also continue the initiative of concerted action to provide regulation for the practice of pathology in its entirety.

Judging by the accomplishment of this Society in its past endeavors, I am inspired to assert that our leadership in satisfying all responsibility for the integrity of the practice of pathology will continue unabated.

A PATHOLOGICAL STUDY OF "SO-CALLED" DENTAL TUMORS*

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From the Department of Pathology, New York University, College of Dentistry, New York City

This study has been made as a result of an analysis of all oral, surgical pathological material received by the Department of Pathology in the last ten years. With few exceptions all this material was removed in our Oral Surgery Clinic. During this period approximately 1800 specimens were submitted, about 1000 of which can be designated as tumors, true and "so-called."

Before explaining the term "so-called," two factors relative to our type of case should be borne in mind: (1) these conditions for the most part were symptomless; the patients presented themselves mainly for trouble with their teeth. The lesions were discovered only by a thorough routine oral examination and (2) most of these patients might be referred to as transients because a very high percentage failed to return after their first two or three visits. This fact obviously increases our difficulty in securing accurate records of these cases.

We have used the title "So-Called Dental Tumors" advisedly in order to emphasize two important features of the material studied: (1) the term "so-called" is used in order to indicate that most of the conditions studied and dubiously classed as tumors are not in reality autonomous new growths, but rather inflammatory in nature and (2) these tumors are labelled "dental" because almost all of the material was obtained from the Oral Surgery Clinic and because they were first seen and diagnosed by dentists as part of their routine clinical work.

Pathologists can readily understand the ease or difficulty in the

*Read before the Fourteenth Annual Convention of The American Society of Clinical Pathologists, held at Atlantic City, New Jersey, June 7 to 9, 1935.

microscopic diagnosis of the following conditions. This seems to us to justify our somewhat arbitrary separation of these tumors

TABLE 1

List A	
EPULIS	245
A. Alveolar border	232
Benign giant cell sarcoma	109
Fibrous	66
Angio-fibromatous	57
B. Central	13
Benign giant cell sarcoma type	9
Osteitis fibrosa	4
CYSTS	400
A. Radicular	226
B. Dentigerous	30
C. Salivary glands	20
D. Nasopalatine	3
E. Unclassified	121
ADAMANTINOMAS	19
ODONTOMAS	15
MIXED TUMORS	3
MALIGNANCIES	81
Low grade sarcomas	5
Lympho sarcoma	1
Carcinomas	72
Salivary gland	9
Squamous	63
Malignant melanomas ?	3
TOTAL	763
List B	
BONE TUMORS (?)	31
ANGIECTATIC TUMORS	20
MISCELLANEOUS GRANULOMAS	70
"SO-CALLED" FIBROMAS (Myxoma-myxofibroma)	30
POLYPS	73
PAPILLOMAS	23
TOTAL	247
	763
GRAND TOTAL	1,010

into two divisions. Those conditions which on microscopic examination are more easily recognized as tumors and more readily classified were placed in list (A); the others in list (B) (see table 1).

EPULIS

Depending on the relation of this condition to the jaw the term "epulis" is used as follows: (1) as an alveolar border growth, peripheral epulis and (2) as a growth within the bone substance, central epulis.

The alveolar border growth or peripheral epulis has its origin in the periosteum, and protrudes from the gum usually between

FIG. 1. BENIGN GIANT CELLS EPULIS

the teeth. The name epulis (ex-pulis) is descriptive of its location. These growths, next to cysts, were the most frequent tumors of the oral cavity.

Pathologically, they appear as inflammatory hyperplasias of connective tissue. Based on their microscopic pictures they may be divided into three groups:

(a) The benign giant cell tumor, paradoxically called benign giant cell sarcoma, is the most frequent and presents the char-

acteristic picture of foreign body giant cells with vascular fibrous tissue. (See fig. 1.)

(b) Fibrous epulis, histologically, is comparable with fibrous polyp. The term fibrous epulis is used when these growths are located on the gums.

(c) Angio-fibromatous epulis, clinically, is similar to the first group but microscopically shows the absence of characteristic giant cells.

Central epulis (osteitis fibrosa cystica)

In thirteen cases from single, localized, rounded masses located in the center of the mandible or maxilla, we found, histologically, evidence of a local osteoclastic process. In confirmation, all on pre-operative x-ray examinations revealed a varying degree of radiolucency. Here we feel that the microscopic picture both of central epulis and localized osteitis fibrosa represents different stages of this osteoclasia and therefore we group them together.

The first group microscopically showed evidence of osteoclasia with proliferation of bone elements, evidence of hemorrhage and an unusually large number of foreign body giant cells. This corresponds to the older and classical picture of central epulis, and represents an active osteoclasia.

The second group, which was characterized by an absence of the giant cells, showed only hemorrhage, cystic changes and bone fibrous tissue proliferation. This picture of osteitis fibrosa cystica is interpreted as representing the healing stage of the osteoclastic process of which central epulis may be the forerunner.

The third or intermediary group showed an essentially similar picture to the above two groups but was characterized by the presence of only a few giant cells.

Further studies of these thirteen cases disclosed eleven females and two males; their ages varied from fifteen to forty-six. There was no one site in either jaw which was characteristic of the lesion. (See fig. 2.)

CYSTS

The cysts of the mouth which we have encountered comprise by far the largest group of "so-called" tumors. This group may be subdivided as indicated in table 1.

Cystic adamantinoma and osteitis fibrosa cystica which frequently manifest themselves in secondary cystic changes are not considered with this group. Clinically, one of the outstanding features of most of these cysts (all except group C) is their lack of symptomatology. The diagnosis is usually made on x-ray examination. Histologically they are all, as a rule, of simple epidermoid type. They have a fibrous wall lined with epithelium. Their location, lining and content determine their type. While their etiology is not fully understood, infection and the presence of epithelium are most important in their development.

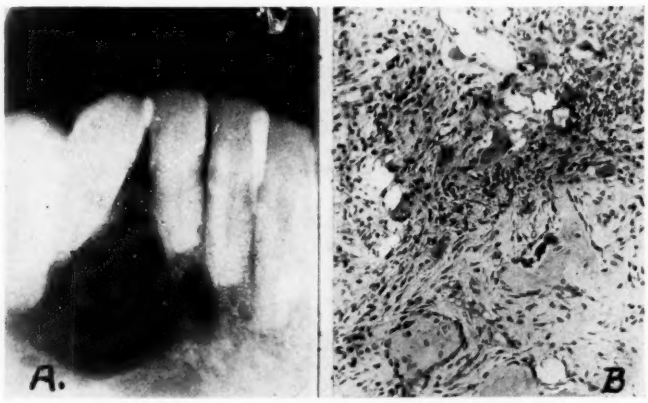


FIG. 2. EPULIS

A. X-ray showing central epulis. B. Photomicrograph showing features of both central epulis and osteitis fibrosa in same field. (Dr. H. M. Seldin.)

Infection. In the radicular or root cysts and in cysts of mucous or salivary glands various evidences of an infectious nature are usually present. In the dentigerous and nasopalatine cysts evidences of inflammation are not as frequently found.

The presence of epithelium. This is usually explained on a basis of "rests" or embryological development. It should be taken into consideration that this is primarily a histopathological study and a satisfactory differential diagnosis as to type can not always be made.

Radicular granulomatous cysts

This constitutes the largest group of cysts. The radicular cyst and the root granuloma have been grouped together because of certain features they have in common, particularly (1) location

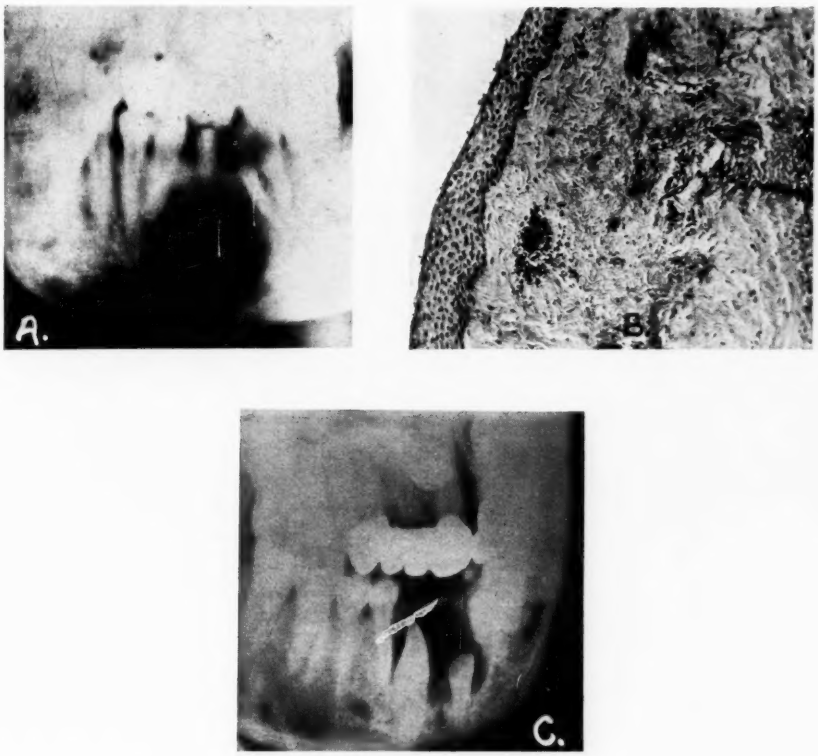


FIG. 3. CYSTS

A. X-ray of radicular cyst at apex of first molar. B. Photomicrograph of cyst wall. C. X-ray of dentigerous cyst containing two unerupted teeth.

at the root of a tooth, (2) evidences of granulomatous reactions in both and (3) our inability at times to differentiate them.

Differences at times exist though they are unimportant. Mainly they are, the smaller size, less probability of signs and symptoms, solidity with lack of cyst formation and at times the absence of epithelial lining in the "pure" granuloma as compared

with the radicular cyst. This group occurs with much greater frequency in males than in females and somewhat more frequently in the upper jaw than in the lower. They are prone to occur in the third and fourth decades.

Dentigerous or follicular cysts

These cysts are embryological in origin, contain a tooth or teeth and arise from misplaced or aberrant tooth follicles. This

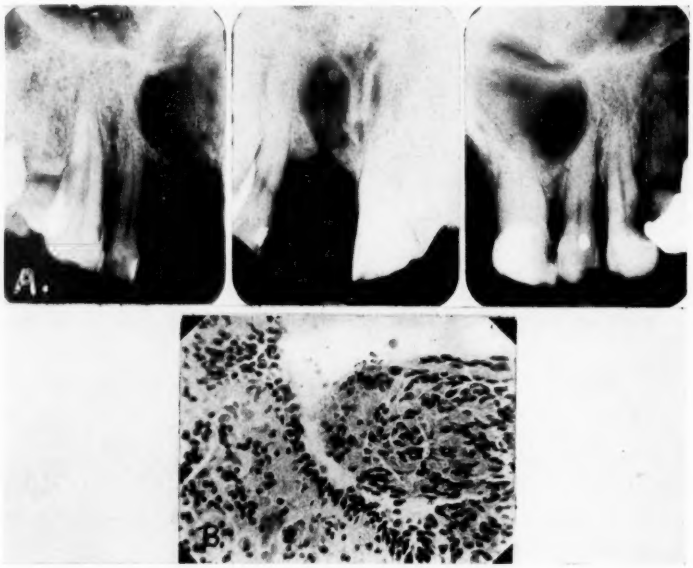


FIG. 4. NASOPALATINE CYST

A. X-rays taken at different angles. B. Photomicrograph of cyst wall. (Montefiore Hospital).

group is decidedly less frequent than the radicular group with both sexes equally affected. The upper jaw is somewhat more often involved than the lower, with a special predilection for the cuspid region being noted. They grow faster and to greater size than the radicular cysts and are more prone to give symptoms. We have had an almost equal number of cases in the second, third, fourth, fifth and sixth decades. (See fig. 3.)

Mucous or salivary gland cysts

Cysts of mucous or salivary glands are also comparatively infrequent. Most of them are found in the floor of the mouth, usually arising from a sublingual gland. Occasionally they are encountered on the palate or lip. Their histories are usually of short duration and in almost all of them evidences of inflammation are present.

Nasopalatine cysts

Nasopalatine cysts, the least common of all these cysts, occur in the median line of the upper jaw and in relation to the nasal cavity rather than to a tooth. They give few, if any, symptoms. On x-ray examination the normal anterior palatine foramen should not be confused with this type of cyst. (See fig. 4.)

Inability to exactly classify cysts in the mouth is largely due to insufficient information. This is because such information has not been submitted or can not be obtained and in this series we encountered 121 such cases.

ADAMANTINOMAS

We are impressed with the fact that this "rare" tumor, if looked for, is not so infrequent. We have had nineteen cases in our series.

An adamantinoma is a true tumor with a fairly characteristic microscopic picture, essentially similar and analogous to basal tumors from which they are a down-growth. Histologically they arise from embryonal rests of adamantine epithelium and show secondary cystic degenerative changes, which usually accounts for their multilocular cystic picture in x-ray.

None of our cases were the solid or malignant type. All were cystic. Only one occurred in the upper jaw. Most of them were in the anterior part of the lower jaw; a few involved the mandibular angle. The majority occurred in the third and fourth decades. These tumors present difficulties in removal, tend to recur and are generally radio resistant. (See fig. 5.)

ODONTOMAS

There are two definitions which are used for odontoma: (1) any tumor which has to do with a tooth or the teeth, (2) a tumor

composed of dentine, cement or enamel. It is obvious that the first definition is too broad. The second definition, the one more widely accepted, still does not fix the condition. The diagnosis of odontoma does not help to specify exactly what the condition is. If one is able to say just what structures are present and the picture is that of enamel, dentine, or cement one should be specific. We believe that many of these conditions of dentine and cement nature are essentially not autonomous new growths but hyperplasias of functional, inflammatory or dystrophic nature, similar

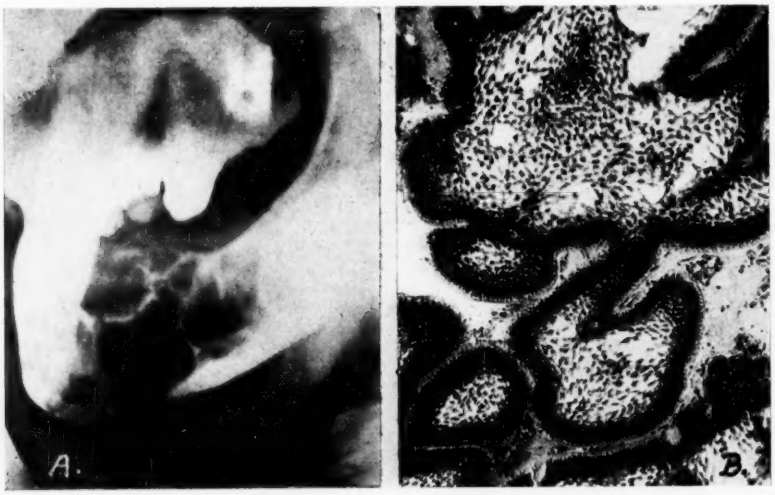


FIG. 5. ADAMANTINOMA

A. X-ray showing multilocular cystic adamantinoma. B. Typical characteristic microscopic picture of a cystic adamantinoma.

to other forms of connective tissue hyperplasias and therefore should not be called tumors.

To us, our main justification for the use of this term has been found in the presence of occasional masses of tooth structure usually mature but some times embryonic. Depending on the maturity of the tooth structure encountered, they may be divided into two groups. While the first is absolutely benign, the second has potentialities which depend on its structure.

Of the first group, irregular masses of more mature tooth structure, we have encountered thirteen cases. (See fig. 6.)

Of the second group, masses of more embryonic tooth structure, we have encountered two most unusual cases. (See fig. 7.)

MIXED TUMORS

Mixed tumors need no comment. In our series we have encountered three cases, one each in the lip, palate and cheek.

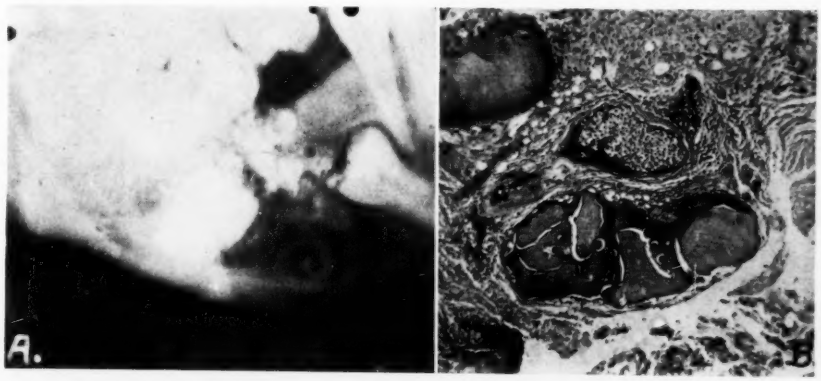


FIG. 6. COMPOSITE ODONTOMA

A. X-ray showing composite radiopaque mass. B. Photomicrograph showing masses of cemento-dentine and nest of tooth anlage epithelium.

MALIGNANCIES

We have considered these tumors under the four groups indicated in table 1.

1. Connective tissue malignancies

A. True sarcoma. In this series we have not encountered one case which can be compared with the connective tissue malignancies we find in long bones or other connective tissue sites.

B. Low grade sarcoma. We have encountered five cases which we called low grade malignancies of connective tissue. As a rule, they tend to grow slowly, invade, destroy and recur. The loca-

tions for these have all been in connection with bone and histologically they can be classed as fibrosarcomas.

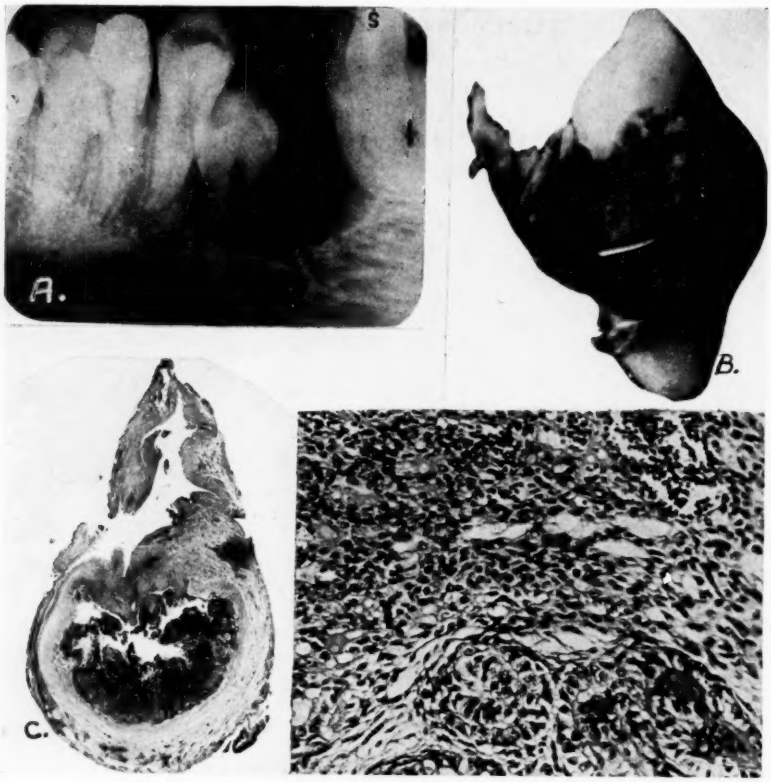


FIG. 7. SOFT ODONTOMA, CYSTIC

A. Postoperative x-ray showing cyst. B. Tooth with tumor attached. C. Cross-section relationship showing of cyst and tumor. D. Photomicrograph of cyst wall showing structures of embryonic anlage of tooth.

2. Lympho sarcoma

One case occurred in a girl seven and a half years of age and involved the upper jaw in the region of the antrum. This child died in about seven weeks after first symptoms of the tumor and upon necropsy, a diagnosis of Sternberg's disease was made. (See fig. 8.)

3. Carcinomas

A. Salivary gland type of carcinoma. This group constitutes a small but definite percentage of epithelial malignancies in the mouth. We have had nine cases. Although similar to mixed tumors, they should be differentiated from them. The salivary gland type of carcinoma is characterized by a greater tendency to more duct and glandular formation, a lack of myxomatous and cartilaginous changes and a more malignant behavior. These tumors should also be differentiated from the most common

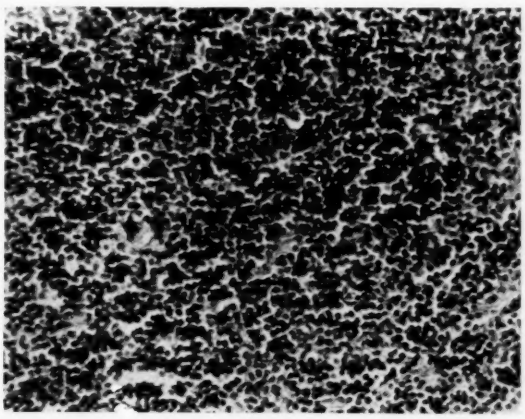


FIG. 8. STERNBERG'S DISEASE

Photomicrograph of biopsy from upper jaw. Diagnosis at necropsy, two weeks later: Sternberg's disease.

epithelial malignancies of squamous type. Other than histological differences the salivary gland carcinomas occur at a decidedly younger age, either sex is affected (six females and three males) and they are rather prone to occur in the upper jaw; especially the palate. (See fig. 9.)

B. Squamous cell epidermoid carcinoma. Our series presents a surprisingly large number of such growths. While a few of these were carcinoma of the lip and tongue, locations which are usually associated with the mouth, a large majority were growths in gingival tissue especially lower gum with involvement of the

adjacent floor of the mouth. A few were of the cheek, palate and antrum. This group is found almost entirely in males. Clinically almost all of these patients were unaware of the serious nature of their lesion. Many of these patients gave evidences of chronic irritation such as rough tooth edges and ill fitting dentures, and several gave a story of "tooth loose, wound failed to heal following extraction."

4. Malignant melanomas

As a result of our very limited experience with tumors in the mouth showing melanin, we prefer to place them in a separate

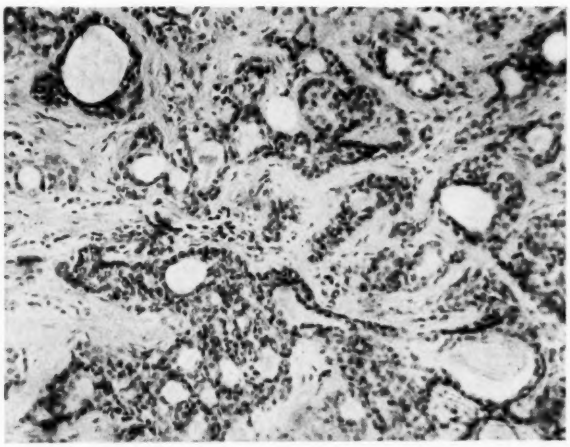


FIG. 9. SALIVARY GLAND TYPE OF CARCINOMA

special category. This is because of our difficulty in saying with certainty whether they are benign or malignant, and whether they are primary or secondary in the oral cavity.

All three of these cases were in the upper jaw. Two were white males, one was a negress; the ages were sixty-three, thirty-four and thirty-two. Histologically, the presence of so much pigment in two of them made the study and interpretation of tumor cells difficult. Case 1, which we were unable to follow showed an invasive and extensive growth both clinically and histologically. Case 2 has run a malignant course. Case 3 has

been under observation such a short period of time that its outcome can not be stated with reasonable certainty at present. It is our reaction from this decidedly limited experience that a very

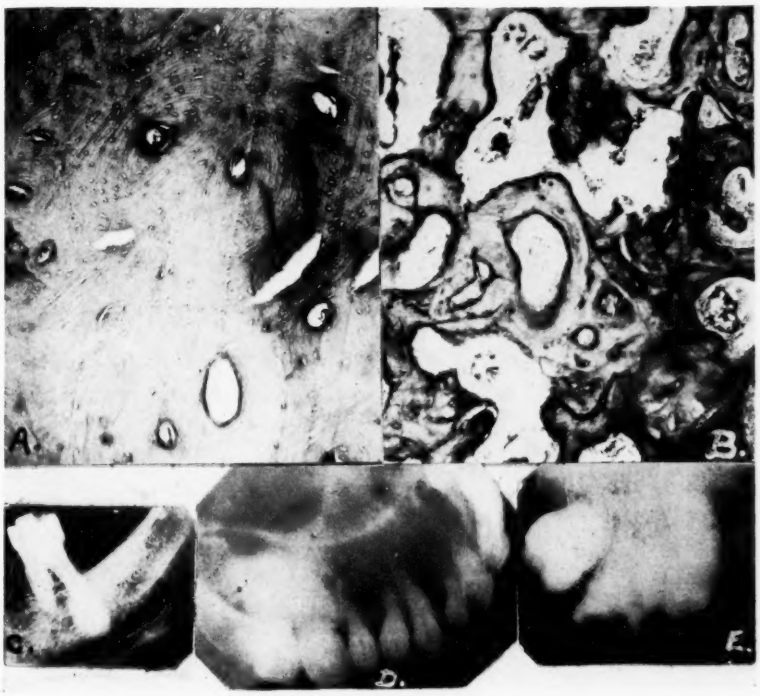


FIG. 10. BONE, PATHOSES

X-rays and photomicrographs illustrating difficulties in interpretation of bone pathoses. A. Lesion such as may be found in condensing osteitis, exostosis and osteoma. Such areas are found in lesions illustrated by roentgenograms, C and D. B. Lesion such as may be found in condensing osteitis, bone dystrophy, exostosis and osteoma. This pathology is found in cases illustrated in roentgenogram E.

guarded prognosis from histological studies alone, should be made as to whether such growths are benign or malignant.

In concluding with this group of malignancies, it should be borne in mind that, if we make a comparison of such types of lesions in other parts of the body, we are impressed with the fact

that these growths in the mouth show local extension and local metastasis rather than distant metastases, and the complications of intercurrent hemorrhage and infection are generally responsible for the patient's death.

Microscopic studies alone do not lend themselves toward so exact a diagnosis in the case of tumors listed under B in table 1.

BONE TUMORS

The differentiation, pathologically, between bone tumors and other osseous lesions, is at times difficult and often impossible.

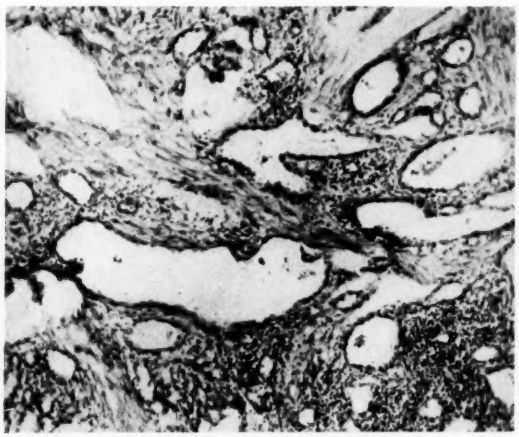


FIG. 11. ANGIECTASIS

Hyperplasias and hypertrophies (of bone) dystrophies and inflammatory lesions may present microscopic pictures comparable to those found in bone neoplasms. We have encountered thirty-one cases in which, we feel, the microscopic features are compatible with a diagnosis of tumor. They are usually benign, occur in older people and are many times symptomless. (See fig. 10.)

ANGIECTATIC TUMORS

In view of the fact that exuberant granulation tissue is an unusually common finding in the mouth, the differentiation on

histological evidences alone between such a change and other angiectatic lesions is difficult.

Because in granulation tissue, granulomas, some so-called endotheliomas, and angiomas the main microscopic change is a proliferation of vessels, the difficulties on microscopic diagnosis are obvious.

Although clinically these lesions appeared as localized vascular masses, we feel the majority of them represent inflammatory neoplasms. (See fig. 11.)

MISCELLANEOUS GRANULOMAS

While granulomas occur at the roots of the teeth in association with radicular cysts previously discussed, it should also be realized that granulomas occur at the roots of the teeth where there is no evidence of cyst formation. Many of these lesions give no signs or symptoms and are so small that they are difficult to detect even with x-ray. When not recognized, they are found only on close inspection of the apex of the tooth after its removal. In addition granulomatous lesions are found in the soft tissue of the mouth, for example, the gums and lips.

Histologically, granulomas are made up of a fibro-vascular matrix containing large numbers of cells of round cell or polynuclear type. The principal cellular reaction we have encountered in lesions of this type are essentially lymphocytes or reticulo-endothelial cells or rarely, polynuclears. Two important modifications or derivatives of reticulo-endothelial cells are foam cells and giant cells. They are associated with an unusual accumulation and precipitation of fatty or lipoid material. On many occasions this fatty material takes the form of cholesterin. It is here that the typical foreign body giant cell reaction is found.

This group is clearly of inflammatory origin.

"SO-CALLED" FIBROMAS

Most of these so-called tumors we feel are inflammatory hyperplasias. When such a process involves fibrous tissue and manifests itself in a localizing mass, the response is obviously a fibroma, myxoma or myxofibroma. It also can be noted here, that if bone

tissue is concerned, the prefix or suffix osteo- distinguishes the nature of the response.

True fibromas while extremely rare in this vicinity should be and can usually be differentiated by their more distinct microscopic "whorl" appearance and sometimes their encapsulation.

Many similarities between fibromas and varieties of epulis and polyp can be made. These are considered in the discussions of epulis, polyps and papillomas, and can best be appreciated by reference to table 2.

POLYPS

Similar to polyps elsewhere, these "so-called" tumors appear as localized finger-like projecting growths. In the mouth, their more frequent locations are cheek, palate, tongue and lip. They are rather frequent and more prone to occur in women. As a rule, they appear with increasing incidence after twenty years of age and give a history of long duration with few symptoms, which factors point significantly to their inflammatory nature. They may have a pedicle or a sessile base and histologically show inflammatory hyperplasia of the underlying tissue over which a thinned compressed epithelium may be found. The majority are distinctly fibrous, but many are quite vascular and are correspondingly more active. Varying degrees of associated inflammatory features of primary or secondary nature may be present.

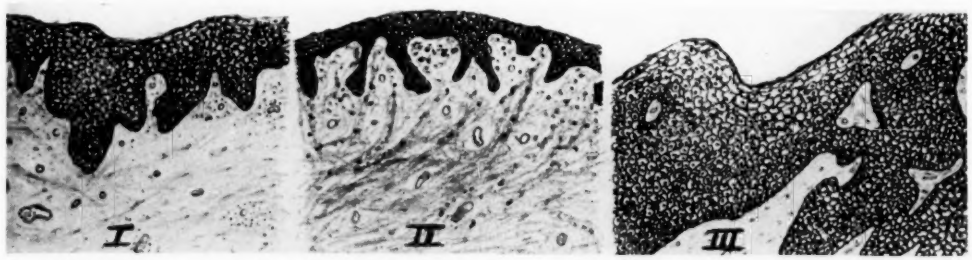
Although benign, following removal, they may recur. We believe that in most cases these so-called "recurrences" are due to a persistent and uneradicated inflammatory focus. As a class they are like nasal polyps, those of the lip or even of the palate may contain glands. When similar types of growths occur on the gums they are classed as epulis. While hypertrophic gingivitis is on occasion polypoid where possible, polyps, epulis and hypertrophic gingivitis should be differentiated.

PAPILLOMAS

The term papilloma should be used to denote a benign growth of the epiderm whose main feature is branching. It should be appreciated, however, that many kinds of tumors and even inflammatory responses may show a papillary structure.

TABLE 2

DIFFERENTIAL FEATURES OF POLYPS AND PAPILLOMATA



	I	II	III
Microscopic pattern	Relatively equal hyperplasia, hypertrophy or increase of both epithelium and corium	Hyperplasia or hypertrophy of fibrous tissue tending to thin out overlying epithelium	(Papillary) hyperplasia or hypertrophy of the epithelium at expense of stroma
Conditions in which such pictures might be found	Papilloma* ↑ Polyp ↑ Normal gingiva	Papilloma Polyp Fibrous epulis Gingivitis	Papilloma Regenerative epithelium as post inflammatory i.e., edge of ulcer In association with malignancy
Frequency	Frequent	Very frequent	Infrequent
Behavior	Benign	Benign	While benign, potentially malignant

* If a papilloma is, according to accepted definition, a benign autonomous epithelial new growth which branches, it can readily be seen that I and II should never be called papillomas.

They are not especially common in the mouth. Most of the reported so-called oral papillomas are not true epithelial tumors but rather inflammatory hyperplasias of connective tissue and epithelium and should be called polyps. Table 2 and the diagrams will help to explain the situation. These may aid in a better understanding of the difficulties encountered not only in the diagnosis and differential diagnosis of polyps and papillomas but also help understand other frequent oral microscopic pictures which these two conditions may histologically resemble and, with which they can be confused.

SUMMARY AND CONCLUSIONS

(1) We have been impressed with the neglect of the oral cavity by general pathologists.

(2) There is an excellent opportunity for the study of pathoses in lesions of the mouth as for example: (a) in connection with the difficult subject of bone. Here is a site in the body more accessible to clinical observation, x-ray and biopsy, and (b) the same thing may be said in regard to carcinoma.

In the presentation of this study the especial coöperation of Drs. L. Winter, L. Hayes, I. Salman and L. Allen of the Oral Surgery Department and Dr. A. Greenfield of the X-ray Department is gratefully acknowledged. The photographs were made by Mr. Alvin Taylor.

THE DETERMINATION OF IRON IN MINUTE AMOUNTS OF BLOOD

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The use of the photo-electric scopometer[1] to determine hemoglobin as acid hematin in as little as 0.1 cc. of blood with rapidity and at the same time with a high degree of accuracy has already been described.[2] The same instrument is well adapted to the determination of iron in biological materials on very small samples or when present in very minute amounts. The method for the determination of ferric iron in blood samples of 0.1 cc. volume has been in use since 1932 in the laboratory of the Prudential Insurance Company. The saving in time and the reliability of results have been very gratifying.

METHOD

Sampling

The blood sample is measured in a capillary pipette, made to contain 0.1 cc. The pipette must be thoroughly clean and dry. When the sample is drawn into the pipette it should rise only a few millimeters above the calibration mark, just far enough to allow adjustment to this line, as wetting the pipette much above the mark will increase the error in sampling. The pipette tip is wiped free of all blood on the outside with moist soft paper, after tilting it to let the sample run back to make a few millimeters of clear space near the tip. The blood column is then brought back to the tip by holding the pipette in a slanting position and the blood is removed to the calibration mark by touching the tip very lightly with absorbent paper with the pipette held horizontally. When the sample is thus measured, the pipette is again tilted to draw the blood away from the tip, the upper end is covered with the finger and the pipette inserted to the bottom of a 15 cc. conical pyrex tube containing 0.5 cc. of water. The blood is allowed to flow under the water, and as much as possible is driven out by repeatedly pressing and releasing the finger on the upper end of the pipette. Finally the tip is lifted into the clear aqueous layer, a portion of the water is drawn in to

rinse it, and then it is drained. If the blood is carefully sampled in this way it should measure 0.1 cc. with an error of less than 1 per cent. The sampling must be done with the greatest care since this is the limiting factor in the precision of the method.

Digestion

The digestion of blood to free the iron from the organic material follows the same technic as the digestion of blood for total nitrogen[3] but instead of using the wet combustion tube employed for nitrogen digestion, time and sample are saved by using the 15 cc. conical centrifuge tube mentioned above. To the blood in 0.5 cc. of water in this tube is added 0.5 cc. of an acid digestion mixture consisting of 100 cc. of concentrated sulfuric acid and 160 cc. of 60 per cent perchloric acid, made to a total volume of 500 cc. The tube is now heated over a micro burner, being so manipulated that the flame plays on the glass at the meniscus, hastening the evaporation of water, preventing foam and catching spray. The material is digested until it becomes charred, and the solution is then cleared by adding 4 drops of strong hydrogen peroxide solution (perhydrol), the tube being held as nearly horizontal as possible and the drops added at "four opposite sides." When the perhydrol reaches the highly concentrated acid solution it begins to steam and spatter and thus cleans the inside wall of the tube, so that the whole mixture clears after a little more heating. With care, there need be no loss through spattering.* When the solution is entirely clear, another drop of the hydrogen peroxide solution is added very cautiously, again holding the tube almost horizontally as this final drop makes more of an explosion than the former ones. When the solution is again clear, the excess moisture will have been driven off, and the iron will be present in the solution in inorganic form. The time required for complete digestion is about 7 minutes.

Development of color

The development of the well-known red color with thiocyanate requires an acid medium, but for this delicate quantitative test accuracy requires that the concentration of the acid should be between 0.6 and 1.8 per cent. This is easily secured by complete neutralization of the digestion mixture and the addition of a measured amount of concentrated hydrochloric acid. For this adjustment of acid concentration there are added to the cooled digested sample in the pyrex tube, 0.5 cc. of distilled water and 3 cc. of 2 N sodium hydroxide solution as nearly iron free as possible. Since the SO_4^{--} ion tends to inhibit the development of the color, an excess of Na^+ ions should be present.

The solution is then neutralized with concentrated hydrochloric acid dropwise, using a standard dropping tube** and phenolphthalein as indicator. When

* Before skill is acquired, the use of the wet combustion tube described for nitrogen digestion is safer.

** The selected glass tubes are 170 mm. long, 5.5 ± 0.1 in diameter, and 3.2 ± 0.05 mm. bore. The end is cut square and ground. A drop of distilled

the pink color disappears, two more drops of the concentrated acid are added. The range of acidity which is safe lies between one and four drops, so the addition of two drops allows an ample margin of safety in both directions.

To the mixture in the tube, 0.5 cc. of 3 N potassium thiocyanate is then added, whereupon the brownish color gives evidence of the conversion of the ferric iron to ferric thiocyanate. Since the color of the ferric thiocyanate is not stable in the acid solution, thiocyanate should not be added until the test can be carried to completion.

Extraction of ferric thiocyanate

The tube containing the solution should now be fitted with a clean cork which will seal it perfectly but extend only a little way below the top of the tube, to expose as little surface as possible to the solution. The cork should be of good quality with no large porous surfaces.

To the solution, 4 cc. of iron-free amyl acetate, is now added from a burette, to insure very accurate measurement. (This should be kept in glass, not tin, to prevent possible iron contamination.) The tube is then corked and the solutions mixed by reversing the horizontal position of the tube gently fifty times. This insures thorough extraction without the formation of an emulsion.

The ester layer is now separated from the aqueous one, using a pear-shaped 30 cc. separatory funnel with short stem. The ester layer is transferred to a clean dry graduated 15 cc. centrifuge tube and the aqueous layer returned to the original tube.

Second and third extractions are made in the same manner, but using only 3 cc. of amyl acetate each time. The centrifuge tube, now containing 10 cc. of the amyl acetate solution (plus a few drops of the aqueous layer settling to the bottom of the tube) is placed in the centrifuge and rotated for two or three minutes at high speed to separate any of the aqueous portion remaining as fine drops in suspension. With proper care the combined extracts, measured in the graduated centrifuge tube, will give a volume as close to 10 cc. as these tubes can be read. If the readings are to be made at once, the small amount of the aqueous portion may be left undisturbed, but if it is desired to keep the solution more than one hour, it is highly important that every trace of the aqueous portion be removed as it causes the color density to decrease appreciably after an hour or two. If the amyl acetate solution is entirely separated from the aqueous layer, the color will persist unchanged for at least 24 hours. The tubes should be stoppered with clean cork stoppers at all times to prevent evaporation and dust contamination. One cannot be too vigilant in the matter of iron contamination. All glass ware must be *freshly* cleaned and all dust in the air prevented. Without a special dust-free room and hood, there is always great danger of contamination.

H_2O by this tube is 0.0781 ± 0.0005 and a drop of urine with 60.01 dynes σ is 0.0630 ± 0.0005 cc.

Amyl acetate is remarkably efficient in extracting the ferric thiocyanate. Study of a large number of immiscible solvents showed that the most efficient were amyl acetate, butyl alcohol and butyl acetate. Amyl acetate was chosen as the most practical. By keeping the aqueous solution small in volume and making the ester extraction with three successive portions there is assured complete extraction of the iron. About 90 per cent is removed by the first 4 cc., almost none remains after the second, and the faint tint in the third (if any) comes from the washing of the previous portion from the sides of the glassware. Repeated tests have shown that when the conditions are properly fulfilled, a fourth extraction will not add enough of the iron salt to affect the reading. If in any case it should do so, the entire test should be repeated.

Calibrating the scopometer

The photo-electric scopometer is calibrated by making determinations on known samples, following in every detail the method to be employed on the sample to be analyzed. In the work here described, 104.98 mgm. of standard iron wire (Baker-Adamson standard wire, 99.86 per cent Fe) weighed on a semi-micro balance sensitive to 0.001 mgm. were brought into solution as $FeCl_3$, the usual precautions being taken to have all the iron in the ferric state. The iron was kept in this state by making the acidity of the final volume (100 cc.) not less than 10 per cent. From this solution dilutions were made with 10 per cent hydrochloric acid, giving known samples containing from 0.05 mgm. to 1.2 mgm. per 100 cc. Portions of these, measured with 0.1 cc. pipettes, were then treated exactly as the blood samples.

The scopometer readings, as scale numbers, are plotted as ordinates against the concentrations as abscissas on cross section paper. On a paper with 1 inch divisions subdivided into tenths of inches, 1 scale number and 0.1 mgm. of iron respectively were assigned to each 0.1 inch. The successive readings thus plotted, give a smooth curve. Determination of about 10 points at approximately equal intervals, from 0.05 to 1.2 mgm. will give sufficient data to locate the curve (see fig. 1).

Reading the scopometer

About 4 cc. of amyl acetate are poured into a clean, dry specimen cup which is then placed in one of the two optical arms of the scopometer, and there given sufficient clearance between the light beam and the meniscus. The scopometer scale (attached to the measuring diaphragm) is set at zero and the galvanometer also brought to zero by means of the adjusting shutter.

The color of the ferric sulfocyanate in amyl acetate fades if left standing in a strong light; hence readings are made immediately the cup is in place. This loss in color density is recovered slowly but completely if the solution is allowed to stand in dull light. It is always best, however, to make a second reading very quickly on a fresh portion with the measuring diaphragm near the end point at the start. The optimum range of reading is between 200 and 600 on the

scale. In determining ferric iron in 0.1 cc. samples of blood in 10 cc. amyl acetate, the equivalents of these scale readings will be found to include the range between 4 mgm. and 24 mgm. of iron per 100 cc. of blood. The iron values corresponding to the scopometer scale readings are found on the calibration chart.

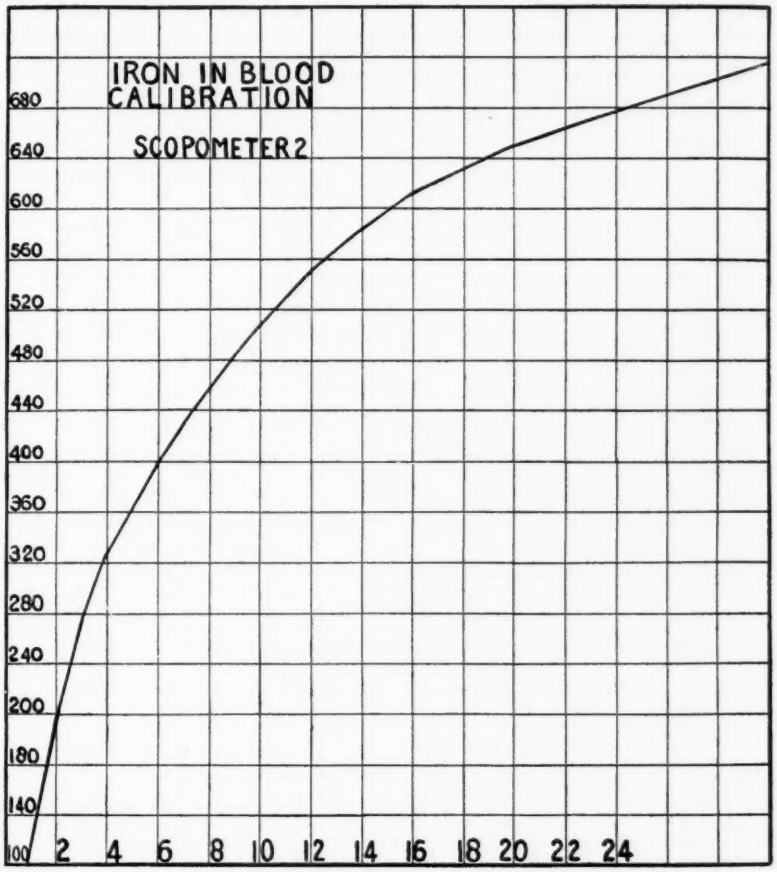

FIG. 1. CURVE SHOWING CALIBRATION FOR IRON IN BLOOD
The iron is expressed as grams hemoglobin per 100 cc. blood

RELIABILITY OF RESULTS

The personal equation is entirely eliminated from colorimetric measurements when color density is recorded by a scopometer. In table 1 are shown the scopometer readings and iron values for

twelve determinations, made in sets of four at three different times on pure solutions of relatively high concentrations for sco-

TABLE 1

IRON VALUE EQUIVALENTS ON SCOPOMETER SCALE OF TWO SOLUTIONS

SOLUTION CONTAINING 50 MGM. PER 100 CC.		SOLUTION CONTAINING 25 MGM. PER 100 CC.	
Scopometer Reading	Iron	Scopometer Reading	Iron
	mgm. per 100 cc.		*mgm. per 100 cc.*
503	49.8	365	25.4
506	50.0	362	25.0
508	50.2	358	24.5
507	50.1	361	24.9
508	50.3	363	25.2
507	50.1	361	24.9
506	50.0	358	24.5
507	50.1	360	24.8
502	49.7		
508	50.2	Average.....	24.9
503	49.8		
508	50.2		
Average.....	50.04		
Average deviation, 0.13 error, 0.25 per cent		Average deviation, 0.20 error, 0.8 per cent	

TABLE 2

IRON DETERMINATIONS ON BLOOD SAMPLES IN WHICH THE MEASUREMENTS WERE MADE ON THREE SCOPOMETERS

BLOOD SAMPLES	SCOPOMETER		
	2*	326	327†
1	37.0	35.6	36.0
2	41.0	41.6	41.0
3	38.5	40.3	39.5
4	41.6	40.3	39.8
5	41.6	41.5	40.6
6	41.8	41.5	40.6
7	42.0	42.3	42.0

* Earlier model.

† From another laboratory.

pometer readings, namely one set containing 50 mgm. of iron per 100 cc. and another containing 25 mgm. per 100 cc. in eight

tests made at four different times. That these satisfactory results are not a chance virtue of the instrument used for most of this work is evident from seven samples measured on three different instruments (table 2). All seven sets agree to about ±1 per cent.

TABLE 3

DETERMINATIONS OF HEMOGLOBIN WITH THE SCOPOMETER BY THREE DIFFERENT METHODS ON EIGHT SAMPLES

SAMPLE NUMBER	HEMOGLOBIN FROM ACID HEMATIN	HEMOGLOBIN FROM FERRIC IRON	HEMOGLOBIN FROM FERRIC IRON IN HEMATIN PRECIPITATE*
	mg. per 100 cc.	*mg. per 100 cc.*	*mg. per 100 cc.*
1	17.6	17.0	17.6
2	18.3	17.4	17.4
3	18.2	18.4	
4	19.8	19.0	19.5
5	17.1	17.1	17.8
6	15.6	15.3	14.1
7	17.2	16.9	16.5
8	16.2	16.2	16.2

* Hemoglobin values usually determined by measuring acid hematin may also be obtained from the hematin turbidity.[2] The two methods agree very well. The acid hematin is preferred on 0.1 cc. samples but where smaller samples must be used the hematin turbidity is more convenient.

TABLE 4

MEASUREMENTS OF EIGHT SAMPLES OF KNOWN CONCENTRATION WITH SCOPOMETER AND DUBOSCQ COLORIMETER (TWO STANDARDS)

(Results given in terms of mgm. Fe per cc.)

KNOWN CONCENTRATIONS	SCOPOMETER VALUES	DUBOSCQ COLORIMETER VALUES	
		Standard: 0.06 mgm. Fe per cc.	Standard: 0.1 mgm. Fe per cc.
0.050	0.050	0.049	0.031
0.060	0.057	0.060	0.049
0.080	0.080	0.092	0.076
0.100	0.098	0.128	0.098
0.120	0.123	0.180	0.125
0.200	0.195	0.354	0.222

A severer test of the method is the determinations on the same blood of hemoglobin as acid hematin, as ferric iron in an oxidized sample, and as ferric iron in the hematin precipitate. Table 3

shows a series of such determinations on eight different blood samples.

In colorimetry the standards must closely approximate the unknown. While attention has often been called to the limited range over which Beer's law holds true, it is often forgotten in practise. Thus table 4 shows the limited range over which Beer's law holds on six samples of known iron concentration when these are matched against standards 40 per cent apart. Table 4 also shows the deviations between simple proportionality and concentration which are automatically cancelled along with other variables in the scopometer calibrations.

SUMMARY

A method is described for the colorimetric determination of iron in blood as ferric cyanate with the photo-electric scopometer using 0.1 cc. of blood sample. The organic iron is digested to the ferric state, the acidity adjusted to a suitable concentration, and the characteristic red color developed by the addition of potassium thiocyanate.

The ferric thiocyanate is extracted by means of successive small portions of amyl acetate and the colored solution removed from the aqueous portion by means of a separatory funnel. After centrifuging, the colored solution of ferric thiocyanate in amyl acetate is read on the scopometer. The readings are interpreted by means of a calibration curve, established with known solutions of pure iron treated in the same manner as the blood to be tested. Reference to this curve gives the equivalent values of iron in solutions of the same concentration as the unknown, and serves also to correct any error due to traces of iron unavoidably present in the most carefully safeguarded reagents. The method is accurate to ±2 to 3 per cent.

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DIABETES MELLITUS WITH REFERENCE TO KIDNEY PATHOLOGY

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It is definitely known that the kidneys are important organs in maintaining acid base equilibrium. Repeated observations have been described in which kidney insufficiency has developed during supposedly adequate treatment of a severe diabetes mellitus, often resulting unexpectedly in death. John[5] reported a case of diabetic coma with oliguria and later anuria with increase of the different metabolites in the blood and a persistently low CO_2 combining power of the blood plasma and edema of the tissues. The kidney complication was characterized by suppression of urine with low phenolsulphthalein output and high blood urea which ran parallel courses. Coburn[2] stated that renal insufficiency with particular reference to the excretion of acetone bodies was probably the most serious complication occurring in diabetes mellitus. He thought that the excretion of the acetone bodies was more important than their oxidation. He discussed a phase of renal insufficiency associated with ketosis without ketonuria. With ketosis there is an albuminuria and cast formation and often increase of blood urea, oliguria, and anuria. In the patients autopsied nothing abnormal was found in the kidneys.

Warren[9] stated that it is reasonable to believe that the rapidity of the development of acidosis depends not only on the rate and amount of acid body production but also on the amount and rate of their excretion which is closely linked with kidney function. He described a tubular nephritis as a complicating pathological finding. Renal insufficiency may be so marked as to prevent the excretion of acetone bodies in which case a ketonuria may not appear. Nitrogen retention in the blood, showers of casts and albumin in the urine may be marked.

Snapper[7] stated that it was definitely known that the excretion and formation of ammonia by the kidneys was impaired in uncontrolled diabetes and that for 48 hours before the onset of coma, casts of a particular type "coma casts" appeared in the urine. With greater involvement of kidney function less ammonia was produced by the kidneys and also a smaller amount of acetone bodies was excreted.

Stern[8] found that 29.9 per cent of his cases of diabetes mellitus had albuminuria and six cases that died all showed "terra cotta" kidneys. Dunn[3] reported on a patient with diabetes mellitus whose blood sugar was 1490 mgm. per cent, non-protein nitrogen 128 mgm. per cent, creatinin 3.4 mgm. per cent, phenolsulphonephthalein excretion 28 per cent in two hours and a plasma CO_2 combining power of 28 volumes per cent. This case indicated to Dunn an acidosis and kidney pathology obstructing the excretion of acid. Bang[1] in discussing diabetic treatment with regard to renal and hepatic function stated that renal function always seemed to be affected in the presence of ketonuria and ketonemia.

The kidney pathology described by most authors was characterized by a tubular nephritis.[4 6 7 9] The tubular epithelium was swollen and granular with glycogenic and fatty infiltration. Many of these renal cells were large and clear due to vacuolization, and were described by Armanni and Ebstein. Often the lumina of the tubules were all but closed due to the swollen condition of the cells. Albumen and casts were found in the lumina. The glomerular capsule may be thickened and there was an intracapsular exudate and an increase in the number of the nuclei in the glomerular tuft. The chronic kidney changes were characterized by fibrosis, intimal thickening of the blood vessels with hyalinization throughout the kidney tissue.

A clinical study was made of 227 consecutive cases admitted to the University Hospital from 1930 to 1935. The patients were divided into two groups, 204 who were dismissed improved from the hospital and twenty-three who died. A pathological study was made of thirty-one cases occurring from 1919 to 1935 from which necropsy material was available.

Of the 204 patients dismissed as improved from the hospital the greatest number (thirty-seven or 18.1 per cent) occurred at the age period from 50 to 59. In the group of twenty-three cases that died the greatest number (nine or 39.1 per cent) occurred at the same age period (see table 1).

One hundred and ninety-six (96 per cent) of the patients who improved were white and seven (3.4 per cent) were negroes. Of those who died twenty-two (95.6 per cent) were white and one (4.4 per cent) was colored.

Of the 204 patients who improved eighty-four or 41.1 per cent had had diabetes from 1 to 5 years and forty-nine or 24.0 per cent

TABLE 1

AGE DISTRIBUTION OF PATIENTS IMPROVED AND DEAD FROM APRIL 1930 TO APRIL 1935

AGES	LIVING	DEAD
0–9	10	0
10–19	22	1
20–29	28	2
30–39	19	3
40–49	35	2
50–59	37	9
60–69	36	3
70–79	16	3
80	1	0
Total.....	204	23

from 5 to 10 years. Of the second series eleven or 47.8 per cent had a duration of diabetes from 1 to 5 years and two or 8.7 per cent from 5 to 10 years (see table 2).

Family history of diabetes mellitus was obtained in twenty-nine or 14.2 per cent of the improved patients and none in those who died. There were twenty-one cases (10.3 per cent) in the improved group that had gangrene and six cases (26.0 per cent) in the group that died. A past history of kidney disease was noted in five (2.4 per cent) of the improved patients and in four (17.4 per cent) of those who died. A definite hypertension was observed in forty (19.6 per cent) of those improved and in five (21.7

per cent) of those who died. Infection that consisted of oral sepsis, sinusitis, carbuncles, and pneumonia was noted in 107 (52.4 per cent) of the improved group and in ten (43.4 per cent) of those who died. Coma was present at some time in thirty-

TABLE 2

DURATION OF DIABETES MELLITUS

YEARS	LIVING	DEAD
0–0.5	25	1
1–5	84	11
5–10	49	2
10–20	11	3
20–30	3	0
Unknown	32	6
Total	204	23

TABLE 3

DISEASES	LIVING		DEAD	
	Number	Per cent	Number	Per cent
Thyroid	11	5.4		
Nephritis	7	3.4	4	17.4
Fibroids-uterus	4	1.9		
Gall bladder disease	4	1.9	1	4.3
Asthma-bronchial	3	1.5		
Mastoiditis	3	1.5		
Malignancies	2	0.9	3	12.9
Pituitary and polyglandular disfunction	2	0.9		
Pernicious anemia	1	0.5		
Pulmonary tuberculosis	1	0.5		
Paralytic strokes	1	0.5	2	8.6
Ischial Rectal Abscess	1	0.5		
Empyema	1	0.5		
Pneumonia	1	0.5		
Renal calculus	1	0.5		

seven (18.1 per cent) of the improved patients and in ten (43.4 per cent) of those who died. A positive blood serum Wassermann was noted in twelve (5.8 per cent) of the improved patients but in none of those who died. A study of past history of diseases revealed those listed in table 3.

The severity of the diabetes was based upon the blood sugar on admission. The peak of the severity curve in the improved group occurred at a blood sugar level of 240 to 279 mgm. per cent and of the group that died the peak was at a blood sugar level ranging from 190 to 309 mgm. per cent. Ten or 4.2 per cent of the improved group had blood sugar on admission of 500 mgm. per cent or over, of those who died there were three or 13.0 per cent (see table 4).

TABLE 4

SEVERITY OF DIABETES MELLITUS

BLOOD SUGAR	LIVING	DEAD
mgm./per cent		
Up to 120	8	0
120–159	14	0
160–189	23	0
190–219	20	3
220–239	23	4
240–279	39	3
280–309	15	4
310–339	16	2
340–369	8	2
370–399	10	0
400–429	5	0
430–499	9	1
Over 500	10	3
Unknown	4	1
Total.....	204	23

The urinary findings noted were albumin, acetone, diacetic acid, sugar, and casts. Albuminuria was noted in seventy-eight or 38.2 per cent of those improved and eighteen or 78.2 per cent of those who died. Acetonuria was found in 114 or 55.8 per cent of the improved group and in 17 or 73.9 per cent of those who died. Diacetic acid was noted in fifty-nine or 28.9 per cent of the improved patients and in seven or 30.4 per cent of those who died. Urinary sugar was noted in 171 or 83.8 per cent of those improved and in nineteen or 82.6 per cent those who died. Casts were found in the urine of thirty-one or 15.1 per cent of the

improved group and in eleven or 48.0 per cent of those who died (see table 5).

The mortality rate of diabetes mellitus at the University hospital from 1919 to 1930 was 16.0 per cent; from 1930 to 1935 10.1 per cent and for the entire period from 1919 to 1935 the mortality rate was 13.3 per cent.

The kidneys of the thirty-one patients coming to necropsy in whom one diagnosis was diabetes mellitus were studied and classified. They were arranged according to the type of changes found. Four groups appeared.

Group 1. Kidneys showing practically no change from normal. Only two cases were found. One was a woman of seventy years of age whose diabetes was well controlled. She developed a

TABLE 5

URINARY FINDINGS

TEST	LIVING		DEAD	
	Number	Per cent	Number	Per cent
Albumin	78	38.2	18	78.2
Acetone	114	55.8	17	73.9
Diacetic	59	28.9	7	30.4
Sugar	171	83.8	19	82.6
Casts	31	15.1	11	48.0

carcinoma of the colon, and following obstruction a 15 cm. tear occurred in the bowel, and death resulted in a few hours. The kidneys were in good condition, and showed only a very slight amount of cloudy swelling of the tubules.

The second case was a man forty-one years old whose diabetes was well under control. A perforated duodenal ulcer caused death from peritonitis. Microscopically, the kidneys showed a mild cloudy swelling of the tubules.

Group 2. Kidneys in which acute tubular degeneration was the most prominent feature. There were ten cases, three having complicating diseases which could account for the kidney changes. In the remaining seven uncontrolled diabetes was responsible for death. One man had a lung abscess of about two months

duration, and another died of lobar pneumonia. The diabetes was well under control in these two cases. The third died of cardiac decompensation. His diabetes was not well controlled due to poor coöperation.

Six of the remaining seven cases died within 48 hours after entering the hospital in coma, or semi-coma. Three had had symptoms only a few weeks. The ages of these six cases ranged from 25 to 47 years; there was one girl of 13. The remaining patient was a girl 11 years of age, who was in the hospital four

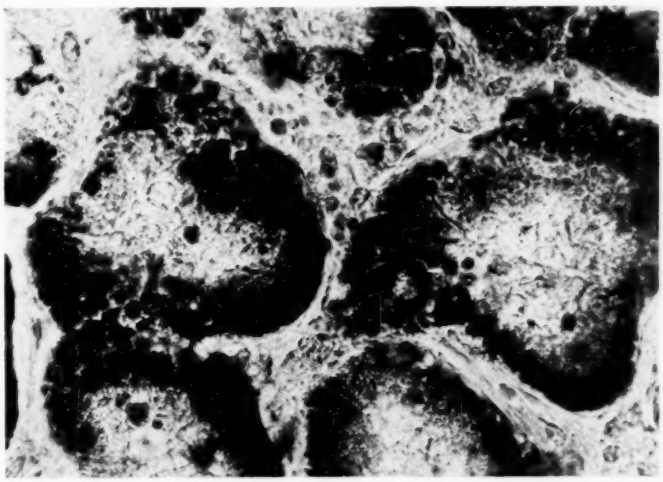

FIG. 1. ILLUSTRATING MARKED FATTY DEGENERATION IN A DIABETIC, POORLY CONTROLLED (CASE 7)

months. Her diabetes was very hard to control, and finally failed to respond to insulin.

The kidneys of this group showed much cloudy swelling of the tubules and all but those from the man dying of cardiac failure showed moderate to large amounts of fat in the lining cells of the tubules (see fig. 1). Several of these kidneys showed Armanni-Ebstein cells (see fig. 2). The glomeruli were appreciably changed from normal in only two. The 13 year old girl, who had diabetes 7 years, showed some increase in the number of nuclei in the glomeruli, and some thickening of the basement membrane

of the tubules. The glomeruli of one 35 year old man showed thickening of the walls of the arterioles. The blood vessels of the kidneys of three showed very slight intimal thickening, and the one previously mentioned had arteriolar thickening.

The islands of Langerhans were studied in all but one case. There was nothing consistent in the findings, although six of the ten showed some change from normal (see protocol).

Group 3. In this group vascular changes were the most prominent lesion. There were seven cases, ranging from 68 to 75 years of age, with one patient 51, who had gangrene complicated by gas

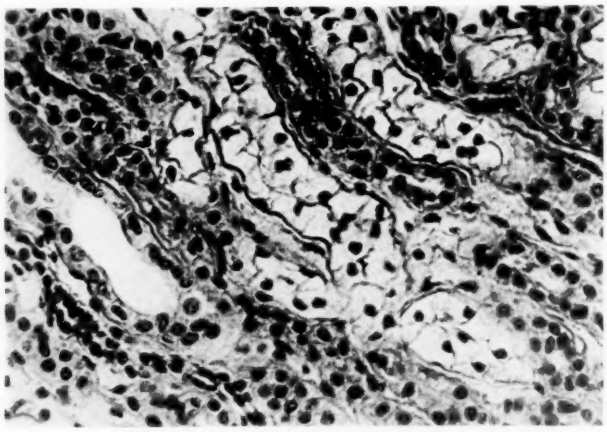

FIG. 2. ILLUSTRATING MARKED GLYCOGENIC INFILTRATION IN TUBULES (ARMANNI-EBSTEIN CELLS) OF A DIABETIC POORLY CONTROLLED (CASE 4)

bacillus infection. These people were known to have had diabetes from six months to fifteen years. Five were controlled without insulin, or with small doses if the disease had been present for some time.

The larger blood vessels of the kidneys showed marked thickening of the walls, especially of the intima, and the smaller vessels were frequently occluded (see fig. 3). Much scarring was evident in the kidneys grossly. Vascular lesions were frequent in other parts of the body, three having gangrene of an extremity, and one having a terminal cerebral hemorrhage. Scarred glomeruli were

found in all kidneys of the group, frequently in rather large numbers. The tubules in these cases sometimes showed evidence of degenerative change, but this was mild in all except one case.

The islands of Langerhan's were examined in all but one of this group, and in only one was there any abnormality seen, a scarring of some islands.

Group 4. Kidneys showing acute inflammatory changes. There were ten cases, ranging from 22 to 71 years of age. Many types of infection were represented. Seven of the group had

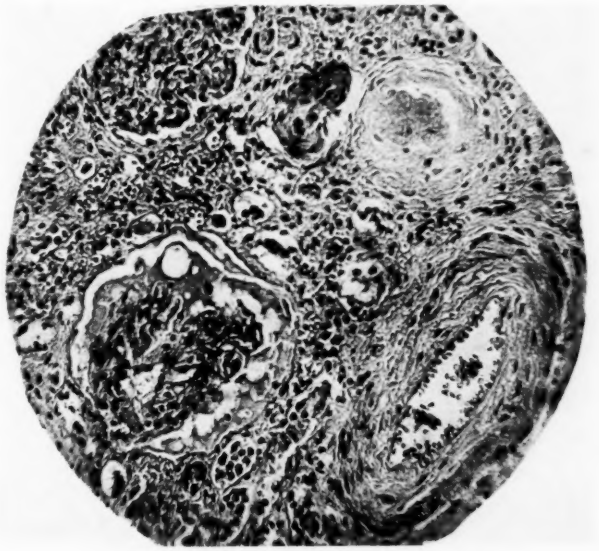

FIG. 3. ILLUSTRATING VASCULAR THICKENING AND OCCLUSION (CASE 11)

elevated blood sugars, and in three cases it was hard to control. Except for these three, the diabetes was kept quite well under control during the period of treatment.

The kidneys of all these patients showed abscesses varying in size and location. In some cases they seemed to spread out from the glomeruli, and in others they were most prominent in the medulla. Mild to moderate cloudy swelling and fatty degeneration were seen in the tubules of a number of cases. The blood vessels of several of the older patients showed some intimal thickening, but it was prominent in only two (see fig. 4).

PROTOCOLS

CASE	AGE	SUMMARY OF HISTORY	GLOMERULI	TUBULES	INTERSTITIAL TISSUE	BLOOD VESSELS	ISLANDS
				Kidneys showing tubular change			
1	46	Diabetes 4 years. Comatose on admission. Dehydrated. Died in 12 hours	Arteriolar thickening, some capsular thickening	Marked granular and fatty degeneration. Armanni-Ebstein cells	No change	Arteriolar thickening	No change
2	46	Symptoms only 6 days. Entered in coma and remained so. Died in 48 hours	Distended, no inflammation	Marked swelling, some fatty change	Much edema	No change	Moderate degeneration of cells
3	11	Diabetes 1½ years. Hard to control, in coma several times. In hospital 4 months	Swollen, tense	Very marked granular and fatty degeneration	No change	Slight intimal thickening	No change
4	13	Diabetes 7 years, one of first here to get insulin. Entered in coma, died in 24 hours	Slight increase in number of nuclei	Much cloudy swelling. Very much fat. Armanni-Ebstein cells. Thickened basement membrane	No change	No change	Cells small, atrophic
5	39	History incomplete. Entered in coma, and died in a few hours	Congestion	Marked cloudy swelling. Moderate fatty change	No change	No change	Fibrosis of all pancreatic tissue
6	43	Diabetes 5 years, controlled. Died of lobar pneumonia	Congested, slight hyalinization	Much cloudy swelling. Some hyalin change	Slight scarring	Slight intimal thickening	Slight fibrosis
7	47	Symptoms 3 to 4 weeks. Entered in coma, and died in a few hours	Swollen	Very marked fatty change	No change	Very slight intimal thickening	Inflammation limited to islands
8	32	Diabetes 1½ years, poor coöperation, not well controlled. Died of cardiac failure. Marked cardiac hypertrophy	Congested	Distended. Cells swollen, granular	No change	No change	Small, few in number, no change in cells
9	35	Diabetes 1 year, quite well controlled. Lung abscess, two months	No change	Very marked granular and fatty degeneration	Edematous	No change	No change
10	25	Diabetes 1 year. Hyperthyroidism, severe 2½ years, treated by X-ray. Heart badly damaged. Comatose on last admission	No change	Marked cloudy swelling and fatty degeneration	Edematous	No change	Hydropic degeneration

Kidneys showing vascular changes

11	70	Diabetes 6 years, discovered after loss of 80 pounds; blood pressure 240; hospital treatment, later disregarded diet. Hemiplegia and convulsions morning of entrance	Many scarred, small vessels thickened	Cloudy swelling. Some fatty change	Areas of scarring throughout	Large and small much thickened	No change
12	75	Weakness four years. Dizziness six months. Cough and fever ten days. Blood sugar, 680 mgm. per cent. Bronchopneumonia, right side	Some fibrosis, others hyalinized. Some crescents	Many thin and irregular, slight fatty change	Patchy increase	Marked thickening, many occluded	Some sclerotic
13	62	Diabetes 15 years. Pain in feet 4 years. Gangrene of toes two months. Leg amputated. Comatose before death	Many scarred and hyalinized	Thin walled, atrophic	Some areas of scarring	Much intimal thickening in medium sized	No change
14	72	Diabetes 2 years. Pain in foot 1 year, discolored two months	Congested, moderate number scarred	Much cloudy swelling	Some increase, narrow cortex	Marked intimal thickening	No change
15	75	Diabetes 3 years. Used 30 units of insulin, but stopped 2 days before entering in coma. Hard to control, in insulin shock three times	Many scarred	Much cloudy swelling, some fatty change	Many scars, some recent	Large and small vessels sclerotic	No change
16	70	Prostatectomy 2 years ago. Loss of appetite 4 days. Convulsions 1 day. Blood sugar hard to control. Had cardiac decompensation	Some scarred	Atrophic, thin	Many large scars	Large and small vessels very sclerotic	Not examined
17	51	Ulcer on foot 6 months led to finding diabetes. Gas bacillus infection not checked by amputation	Some scarred	Slight cloudy swelling	Many small scars	Marked thickening of small vessels walls	No change

Kidneys showing acute inflammatory changes

18	37	4½ months pregnancy; known diabetic 2 months. Pneumonia, with persistent positive blood cultures	Swollen endothelium. Many polymorphonuclear cells	Swollen, granular	Scattered small abscesses	No change	No change

PROTOCOLS—*Concluded*

CASE	AGE	SUMMARY OF HISTORY	GLOMERULI	TUBULES	INTERSTITIAL TISSUE	BLOOD VESSELS	ISLANDS
			Kidneys showing acute inflammatory changes—*Concluded*				
19	40	Abscesses of thigh, drained. Blood culture Staph. albus. Blood sugar, 400 mgm. per cent on admission	Swollen, some increase in polymorphonuclear cells	Cloudy swelling	Scattered abscesses	Some intimal thickening	No change
20	18	Known duration 2 years. Boil on neck with blood stream infection	Swollen, congested. Many involved in abscesses	Granular, fatty, some casts	Many small abscesses	Intimal thickening in small vessels	Not examined
21	46	Diabetes 5, probably 9 years. Pain in hip with abscess 2 weeks	Few scarred	Moderate cloudy swelling	Scattered small abscesses	Slight intimal thickening	Not examined
22	45	Diabetes 3 years. In hospital 4 times, lower sugar tolerance after each break. Very scanty urine. Clinical diagnosis of uremia.	Some scarred	Cloudy swelling, some fatty change	Several large abscesses	Moderate intimal thickening	Not examined
23	43	Diabetes 4 years. Pain in low abdomen 3 weeks. Blood sugar, 1280 mgm. per cent. Cystitis and pyelitis	Many involved in small abscesses	Much cloudy swelling, slight fatty change	Many abscesses	No change	No change
24	71	Duration unknown. Gangrene of foot with infection.	Many sclerotic and obliterated	Slight cloudy swelling	Many scars, small abscesses	Marked intimal thickening, calcification	Not examined
25	48	Diabetes discovered after carbuncle developed on neck. Blood stream infection	Few scarred	Much cloudy swelling, some fatty change	Several abscesses	Arterioles and small vessels thickened	Not examined
26	60	Diabetes probably 3 years. Injury to ankle 1 week previously. Blood culture: *Staphylococcus aureus*	Some scarred	Thin and atrophic	Many abscesses, especially in medulla	Slight intimal thickening	No change
27	22	Diabetes 2 years; 6 months pregnancy. Entered in coma, spontaneous abortion	Some increase in polymorphonuclears	Granular, sloughing	Many abscesses throughout	No change	Some islands fibrotic

The islands of Langerhan's showed practically no change in the five cases where the pancreas was available for study.

There were two cases that hardly fit into the above classification. One, a woman 68 years of age, had a well controlled diabetes for six years. She entered the hospital in semi-stuporous condition, complaining of much pain. Necropsy revealed a retroperitoneal sarcoma, with metastases to all the tissues of the body, and especially noticeable in the kidneys. The other, a man of

FIG. 4. ILLUSTRATING INFLAMMATORY CHANGES

52 years of age, had a glycosuria for six years, controlled easily by diet. Death was caused by chronic nephritis, and cardiac failure. The kidneys were the shrunken, granular organs of a terminal glomerulonephritis.

SUMMARY

(1) A clinical study was made of 227 consecutive cases of diabetes mellitus entering the hospital during the period 1930–1935. Twenty-three of these patients died. A pathological study with

special reference to kidney pathology was made of the thirty-one cases available from 1919–1935.

(2) There was no characteristic age or race distribution, and no significant relation between duration and mortality.

(3) Gangrene was about two and one-half times, history of antecedent kidney disease about eight times, and history of coma about three times as frequent among the patients who died as among the living.

(4) There was no appreciable difference in the incidence of hypertension, or of infection in the two groups.

(5) Urinary albumin was about twice, and urinary casts about three times as frequent among those who died as among the living.

(6) The mortality rate for the period 1930–1935 was 10.1 per cent, for the period 1919–1930, 16.0 per cent, and for the combined periods 13.3 per cent.

(7) There were quite striking kidney changes in most of the cases examined at necropsy, roughly equal numbers showing tubular damage, inflammatory changes, and vascular lesions.

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EPITHELIOID CARCINOMA OF THE PANCREAS WITH DUODENAL HEMORRHAGE

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Adenocarcinomata are undoubtedly the commonest neoplasms arising in the pancreas.[8] The compressing and invading action of such a carcinoma gives rise to many symptom-complexes depending upon the degree of involvement of adjacent structures. The picture of progressive, fairly constant, obstructive jaundice with but little pain in middle-aged or older individuals, associated with mid-upper abdominal tenderness and a palpable mass with ensuing cachexia, is properly accepted as suggestive of an adenocarcinoma of the head of the pancreas. When marked variations in the symptomatology appear the diagnostic possibilities rapidly become illimitable, in view of the large group of established pathological conditions which may develop in the upper abdomen.

The adult gland contains cells composing the excretory ducts and tubules leading from the acini, the larger ducts of Wirsung and Santorini, and the lower end of the bile duct; the pyramidal cells of the acini; the A and B (and possibly D) type of cell of the pancreatic islands (Langerhans); and the cells of connective tissue, blood vessels, lymphatics, and nerves.[9] That the cell types may give rise to characteristic tumors such as the adenocarcinoma of the acinar cells, the cuboidal and cylindrical cell carcinoma of the pancreatic and bile ducts, or the minute adenoma of the B cells of the islands, is, of itself, interesting but the problem becomes exceedingly intriguing when cells of the gland undergo a metaplasia to a type entirely foreign to its normal histological structure. Such a situation exists in the epithelioid or squamous cell carcinoma of the pancreas. The patient in the following case summary was recently referred to me.

CASE REPORT

An Italian male, 45 years of age, a coal miner, entered the hospital February 14, 1935. Because of his lack of knowledge of the English language, a great part of the history had to be verified by questions directed through an interpreter. The patient had but two symptoms: (1) weakness and (2) mild upper abdominal discomfort, both of ten days duration. The onset had been insidious with flatulence and vague upper abdominal distress in the nature of a fullness, unlocalized, aggravated by eating and associated with some belching. Two days after the onset of those symptoms the family noticed a yellowness of his eyes and skin. His physician gave him a purge which seemed to relieve the flatulence and upper abdominal discomfort for about twelve hours. For two or three days prior to his hospital admission he had not eaten, partly because of the increased sense of upper abdominal fullness after taking food and partly because of a loss of appetite. Two days before admission the patient passed a stool that was "black like tar."

The patient's previous health had been excellent. He was in the army during the World War and received a laceration in the right thigh from shrapnel. Of significance in the past history was the fact that the patient had had no previous jaundice, no typhoid or other important fever, no dyspepsia, no upper abdominal pain or colic, no vomiting, and had previously had a normal bowel habit without resorting to laxatives or cathartics. He had had a fairly normal diet, including fruit and vegetables, and his weight had been constant until the week before coming to the hospital when he had lost three pounds. He did not know the cause of death of his mother at the age of 46 years. His father died in an industrial accident at the age of 33 years, and one brother and three sisters were living and well. Beyond the immediate family he knew nothing of the illnesses or causes of death in his blood relatives. This was his first admission to any hospital.

The physical examination revealed him jaundiced and of about 45 years of age in appearance, slightly undernourished for his stocky frame, and with a moderate flabbiness of the skeletal musculature. The blood pressure was 138/90. The positive findings were moderate jaundice of the sclerae, a dental plate replacing the upper teeth, yellowish mucus membranes of the mouth and throat, a yellow hue to the tanned olive pigment of the skin, and a palpable liver edge, smooth and painless, about 3.0 cm. below the right costal margin. On admission, his weight was 74 kg.

Laboratory reports

Daily urine specimens were mahogany in color with only an occasional fluctuation which could be accounted for by fluctuations in the fluid intake of the patient. The stools were a grayish brown to a tar-black color and regularly gave a strong reaction with the benzidine reagent. Only an occasional small amount of bile (by the corrosive sublimate test) could be demonstrated in the feces but undigested fat was present in increased quantities. The icteric index

rose from 23.75 on Feb. 15 to 45.0 on Feb. 23. By March 3, it had risen to 60.0. During the first ten days in the hospital the jaundice deepened to a greenish bronze. The blood non-protein nitrogen on Feb. 15 was 40 mgm. and the blood Kahn test was strongly positive. On Feb. 23, the blood count was: 2,500,000 erythrocytes, 60 per cent hemoglobin, 7,800 leukocytes. On March 3, the count was 1,300,000 erythrocytes with hemoglobin 40 per cent. After the ingestion of 40 grams of galactose (Feb. 15) the patient excreted only 0.8 gram in the urine. An Ewald meal (Feb. 23) showed 38 units of free acid and 58 units of combined acid.

The patient was given barium by mouth on two occasions during his hospital stay and subsequent fluoroscopic observations were made frequently. The chest, heart and great vessels, mediastinum and esophagus were normal. The stomach was the high-lying "steer-horn" sthenic type, with a normally filled duodenal cap lying behind the pylorus in the anterior-posterior view. The duodenal loop described an arc having an internal diameter of about 6.0 cm. with the fluoroscopic screen immediately against the abdomen. There was no tenderness and no palpable mass under the muscular abdominal wall. The barium passed without obstruction through the small bowel and gave a well outlined colon.

The patient maintained a low grade fever, grew progressively weaker and died March 19, thirty-three days after admission to the hospital and only forty-three days after the first symptom of illness. His hospital treatment consisted of saturated solution of potassium iodide by mouth for the first two weeks and two intramuscular injections of bismuth. When it became apparent that the gastro-intestinal hemorrhage was killing the patient, the anti-syphilitic treatment was discontinued. He was given large doses of morphine, three days starvation, and, later, alkaline powders in an effort to check the hemorrhage. There was no hemorrhoidal varix and no vomiting until forty-eight hours before death when he began vomiting blood. He was given normal saline with 10 per cent glucose intravenously and one transfusion of compatible blood.

The patient's blood pressure, which fell to 102/56 by March 14, could not be read a few hours before death. An exploratory operation was not advised because of the unremitting blood loss and poor physical state. The liver receded beyond the costal border before death but the size of the liver, by percussion, was not sufficiently reduced (in the presence of a negative galactose test) to warrant the assumption of liver necrosis as a primary factor in the illness.

A diagnosis of a neoplasm of the papilla of Vater was made prior to death.

Autopsy report

The body is that of a well-nourished Italian male of about 45 years of age. The looseness of the skin of the extremities suggests moderate loss of weight. A deep jaundice of the skin, sclerae and mucus membranes is superimposed on a marked pallor. The scalp and hair are not remarkable. No bruises, unusual surface markings or scars are noted. The body heat is still present.

The abdomen is opened by a mid-line incision revealing an inch and one-half

of panniculus adiposis. A moderate amount of fat is present about the abdominal viscera and in the omentum. A very small amount of free fluid is present in the peritoneal cavity.

The gallbladder is moderately distended by dark viscid bile. The cystic and common ducts are dilated. The wall of the gallbladder is thin and has a bile-stained, smooth, but otherwise unchanged, mucus membrane. There are no calculi in the bladder or duct system. The liver is markedly bile-stained and has a smooth surface. Its lower margin is approximately at the right costal border. The surface made by cutting the liver is granular, dry and composed of many fine white septa separating pin-point areas of yellow brown color.

The head of the pancreas is slightly enlarged, unduly firm, nodular and fixed to the duodenum, adjacent blood vessels and retroperitoneal glands. The firm, cartilaginous character of the head does not extend through the body of the gland. The duodenum is firmly adherent and in removing the head of the pancreas the former structure is left attached. A fresh tubular clot of blood, six to eight inches in length, is present in the duodenal loop. The neoplastic tissue extends about 4 cm. lengthwise and about one third of the circumference of the descending portion of the duodenum. An area of the duodenal mucosa (1.5 x 2.0 cm.) is eroded and covered with fresh blood. The margins of this ulcer are not elevated.

The stomach mucus membrane and the mucus membrane of the lower end of the esophagus is intact and smooth. A few scattered submucus petechiae are present.

Palpation of the pelvic viscera and kidneys shows no alteration. The spleen is approximately 12 x 10 x 5 cm. The surface made by cutting the spleen does not bulge and is not unduly friable.

The thorax and head were not opened, by request of the family of the deceased.

Anatomic diagnosis: Primary carcinoma of the head of the pancreas; carcinomatous invasion of the duodenum with hemorrhage; complete obstruction of the terminal portion of the common bile duct; carcinoma metastases to retroperitoneal glands; early cirrhosis of the liver; petechial hemorrhages into the gastric mucosa; marked generalized icterus.

Histologically, the head of the pancreas is almost completely replaced by the invasion of cells of the carcinoma. These cells vary in size and have deep-staining nuclei which present evidence of rapid mitosis. The tumor tissue shows marked irregularity in arrangement. In only a few places does the tumor form thin strands between fibrous tissue and suggest a scirrhus. Likewise there are but few areas with a tubular or adenomatous arrangement of the carcinoma cells (fig. 1). The predominant arrangement is into whorl-like structures forming larger or smaller "islands" and finger-like projections of tumor extending throughout fibrous tissue and pancreatic parenchyma. In many groups the carcinoma cells are small at the periphery and become larger

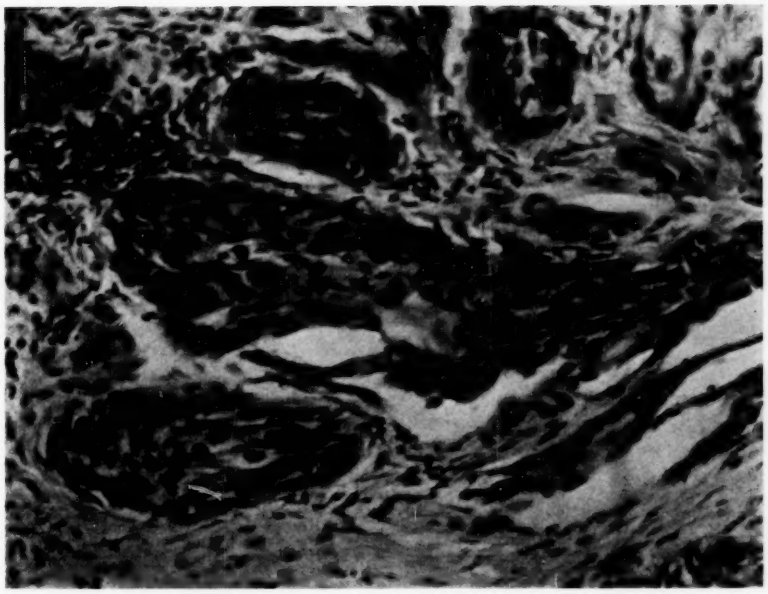

FIG. 1. A PORTION OF THE TUMOR NOT UNLIKE THE USUAL ADENO-CARCINOMA OF THE PANCREAS

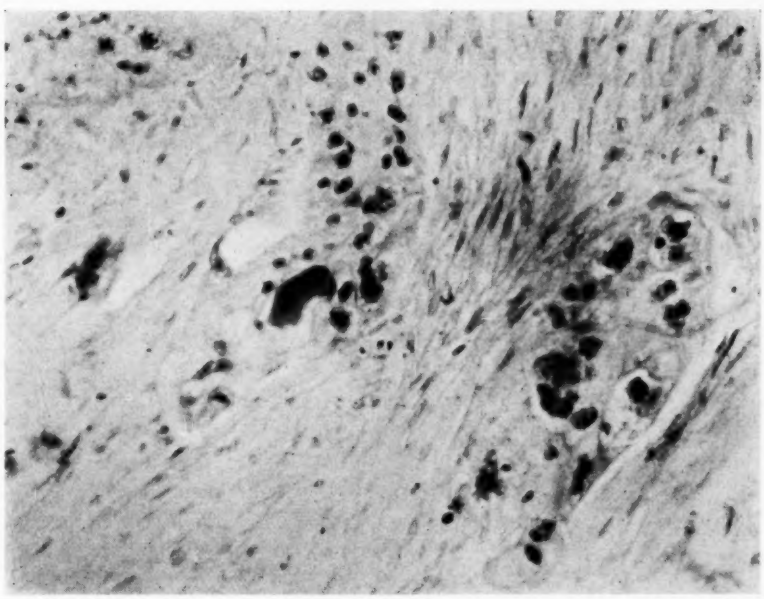

FIG. 2. SMALL GROUPS OF THE EPITHELIAL CELLS LYING BETWEEN CONNECTIVE TISSUE BUNDLES

The intercellular protoplasmic bridges may be noted

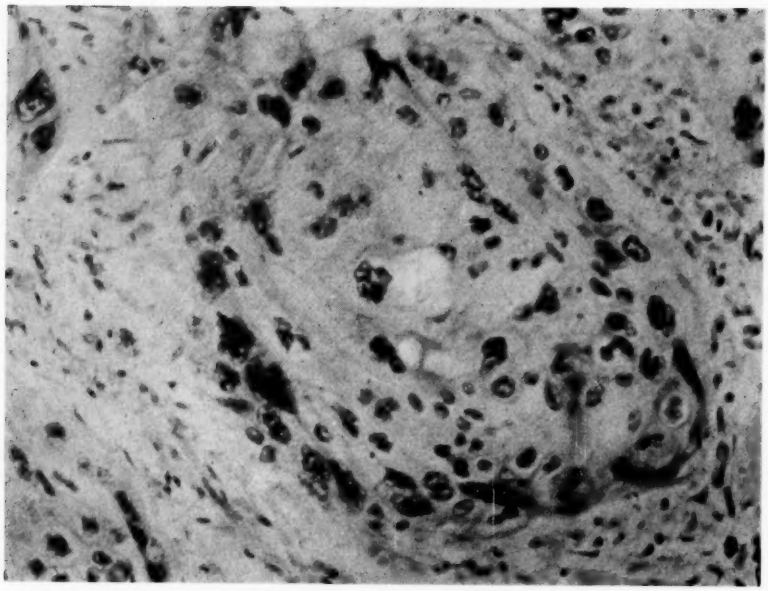

FIG. 3. NEOPLASTIC CELLS ARRANGED IN A WHORL

The section is sufficiently thin to show numerous mitotic figures in individual nuclei. Excess keratin formation (pearls) as well as cellular degeneration may be found in the center.

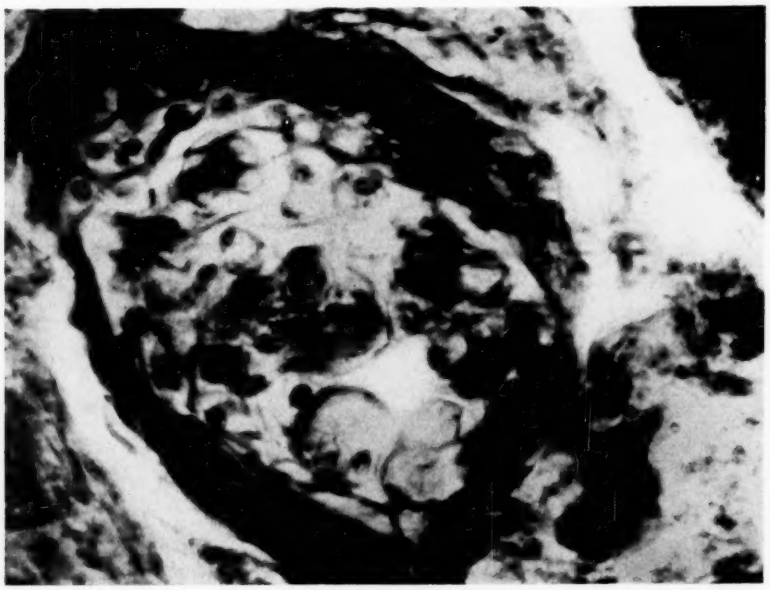

FIG. 4. EPITHELIAL CELLS WHICH HAVE INVADED A VESSEL

(Ca. 400×)

toward the center with protoplasmic bridges between them (fig. 2). In the very center there may be found marked keratinization with displaced and fused nuclear material, with concentric whorls of keratin, and with an occasional well-developed epithelial pearl (fig. 3). Often in the center of other groups of tumor cells there are, instead of compact pearls, cavities lined with keratinized cells and filled with a debris of degenerated and desquamated cells. Several lymph and venous channels are packed with an assortment of tumor cells (fig. 4).

Sections through the duodenal wall at the level of invasion by tumor tissue show the mucosa replaced and distorted by the neoplasm. On the surface next to the lumen of the duodenum there is much blood. There are numerous accumulations of polymorphonuclear leukocytes in the duodenal wall.

In the liver lobules, a considerable distance from the hepatic triads, there is a marked bile stain. There is a moderate increase of connective tissue with accumulations of leucocytes surrounding the lobules. The hepatic canalicules and ducts are markedly dilated and the surrounding liver cells are in various phases of degeneration.

There are no metastases other than invasion of retroperitoneal lymph nodes immediately adjacent to the tumor.

DISCUSSION

The events leading to the death of the patient were remarkable in the brief duration of symptoms and the marked, constant gastro-intestinal hemorrhage. The clinical diagnosis of an ampulla of Vater neoplasm was pure deduction indicated by the lack of evidence of a gastro-intestinal lesion during two fluoroscopic studies. It should be observed in this connection that carcinomas of the head of the pancreas may lead infrequently to profuse bleeding into the duodenum. Adler,[1] in eleven instances of carcinoma of the head of the pancreas in which histologic diagnosis was made, found six patients in whom the tumor mass had ulcerated into one or more hollow viscera. While the stomach, jejunum, ileum and gallbladder were infrequently involved, there were four instances each of ulceration into the colon and into the duodenum. Ochsner and Wilbur[11] observed that carcinoma of the pancreas rarely erodes the duodenal wall. Eusterman,[4] in a review of 138 cases of carcinoma of the pancreas, found but two with perforation into an adjacent portion of the gastro-intestinal tract. Landau[6] found a small duodenal ulceration in the region of a stricture produced by a carcinoma of the head of the pancreas.

The most adequate description of squamous cell carcinoma of

TABLE 1

EPITHELIOID TYPE OF PANCREATIC TUMORS

REPORTED BY	SEX	AGE	JAUNDICE	GROSS TYPE	MICROSCOPIC TYPE	METASTASES
Israel, quoted by Papadopoulos	F.	50	?	Goose-egg size, in the head of the pancreas, at the level of the papilla	Carcinome pavimenteux mixed with strands of columnar cells	?
Lewishon, quoted by Papadopoulos	M.	67	None	Mass 3 cm. in diameter in head of pancreas	Carcinome à epithelium pavimenteux with keratinization and necrosis. Part of the tumor, of cylindrical cells	Hepatic metastases
Herxheimer, quoted by Papadopoulos	F.	65	?	Mass 5 x 6 cm. in tail of pancreas	Epithelium pavimenteux with cornification, epithelial fibrils, and necrosis. Shows columns of epithelial cells	?
Askanazy and Jordanowa, quoted by Papadopoulos	F.	49	Present	Mass in head of the pancreas	Epithelium pavimenteux in flat mosaic and with a few globules epidermiques. Also cylindrical and cuboidal cells	?
Papadopoulos	M.	66	?	Mass 5.5 x 6 cm. in head of the pancreas	Adeno-carcinome pavimenteux	Metastases to liver and pleura

Letulle, quoted by Dominici[3]	M.	70	Present	Mass 1 x 1.5 cm. as a truncated cone in the ampulla of Vater	Groups of flat epithelium with hyaline and colloid degeneration. Some stratification of cuboidal and cylindrical cell types	None
Cornil, Mosinger, Olmer, and Audier[2]	?	61	None	Mass in body of the pancreas, orange size and hard	Epithelioid cells, pseudo-papillary and trabecular arrangements	None
Pollet[13]	M.	70	Present	Mass 1 x 1.5 cm. in ampulla of Vater, with invasion of pancreas	Metaplasia of portions of cuboidal and columnar cells to squamous (?) and other bizarre forms	Metastases to retroperitoneal gland
Lawrence	M.	69	None	Grape-fruit size mass, firm and white attached to stomach and liver, and occupying body of the pancreas	Predominantly of the squamous cell type with marked keratinization and pearl formation	None. A pseudo-encapsulated mass
Plenge, quoted by Henke and Lubarsch[5]	M.	58	?	?	"Cancroid form," with flat cells and keratinization; other areas of cuboidal and cylindrical cells	Metastases to lymph glands, lung, pleura, liver and suprarenals

the pancreas to be found in available literature is that of Lawrence[7] who commented upon the influence of infection and chronic inflammation in relation to epithelial metaplasia in the respiratory, gastro-intestinal and urinary symptoms. Wolbach and Howe[15] have produced in laboratory animals a replacement of various epithelial linings by a clear cut, stratified keratinizing epithelium after deprivation of certain vitamines, especially in the deprivation of vitamine A. They also observed one patient in whom the pancreatic ducts were lined by a stratified squamous type of epithelium. While conditions of tissue culture are highly artificial, it is of interest that Murray and Bradley[10] have noted that tissue cultures of island cell adenomas from human pancreas result in a "pavement epithelium" type of growth.

In table 1 are summaries of ten reports in which apparently true epithelioid type of pancreatic tumors have been proved histologically. The thesis of Papadopoulos[12] contains the four case reports found before 1917. It was his conclusion that the epithelium of the excretory ducts was probably the cell type which becomes transformed directly into a "pavement epithelium" in the origin of these rare squamous cell tumors of the pancreas. Springer[14] pointed out that new growths involving the terminal bile and pancreatic ducts have six principal sources of origin: (1) the common bile duct, (2) the ampulla of Vater, (3) the duct of Wirsung or Santorini, (4) the papilla of Vater, (5) the duodenal mucosa, and (6) the head of the pancreas. The tumor in the present report must have arisen from some structure in the head of the pancreas. The papilla of Vater was of normal appearance and was 0.5 cm. above the flat eroded area in the duodenal mucosa. The microscopic sections through this eroded area eliminate the duodenal mucosa as the source of origin. The terminal bile and pancreatic ducts were compressed but presented no evidence of being the site of origin.

SUMMARY

The case history and post-mortem findings in a patient with obstructive jaundice, who died of a gastro-intestinal hemorrhage six weeks after the onset of illness, are described.

A tumor mass arising in and occupying the head of the pancreas was found to have invaded the duodenum. The histologic structure was that of a well defined epithelioid (squamous cell) carcinoma.

A brief summary is given of other reports of such metaplasia in carcinomas of the pancreas.

The author wishes to express his appreciation to Drs. J. L. Goforth, Dallas, Texas, and George T. Pack, New York City, for their kindness in examining the histologic sections of the case reported. The photomicrographs were prepared by Messrs. P. Irvine and Boyers Clark, Elkins, W. Va.

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SOME ADVANCES IN THE TREATMENT OF TUMORS BY THE X-RAYS AND RADIUM*

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The clinical pathologist has been a most important factor in the study and management of malignant disease. The radiologist has also increased rapidly in importance in the treatment of malignant disease. The choice of treatment in recent years has been influenced greatly by the knowledge of the character of the malignant disease under consideration, as determined by the pathologists. Advances in treatment may be properly considered under four headings: (1) improvements in equipment, (2) improvements in technic, (3) improvements in knowledge concerning selected types of cases, and (4) improvement in results of irradiation therapy.

Radiation therapy is dependent upon the use of either roentgen rays or one of the radioactive substances, particularly radium. These agents can often be used conjointly to advantage, and likewise, must often be used to supplement surgical treatment.

1. IMPROVEMENTS IN ROENTGEN EQUIPMENT

In this matter, I shall only discuss the principles involved in the improvements rather than any individual equipment. With regard to the roentgen ray equipment, the penetrative value has been increased since about 1920 by stepping up the voltage from 125,000 to 200,000. During these past fifteen years, the radiologists have gradually learned how to utilize this increased power. This increased voltage has shortened the mean wave length from 0.23 Angstrom units to 0.16 Angstrom units, and during the past two years, this voltage has been increased to 300,000, 400,000 and

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up to 700,000 volts, but the equipment for these higher voltages is not flexible, and the advantages have not been clearly established, nor the results definitely improved. Theoretically, one may expect definite improvement as the equipment becomes perfected for increased penetration permits increased filtration, and while physicists have not shown us any great advantage of increased filtration, clinical radiologists have observed improvement in results with increased filtration.

Filtration. The filtration used in radiation therapy was started by me in 1905, at which time I made use of sole leather with the object of removing the softer rays which would ordinarily affect the skin. This filtration has been increased gradually to 1 mm. of aluminum, then up to 6 mm. of aluminum, then 0.5 mm. of copper, and now, in certain cases, commonly 2 mm. of copper, or its equivalent in the Thoraeus combination filter. In some instances, this filtration is carried to the equivalent of 5 mm. of copper. When using radium, I commonly use 2 mm. of platinum. These higher filters remove the softer and less penetrating radiation, and enable one to approach the action of the gamma rays from radium. The biological advances of this higher filtration permits us to give a very much greater depth dose of the rays in cancer tissue. They produce a greater differentiation in effect upon diseased tissue as compared with the normal, and therefore, enable one to produce a definitely destructive effect upon the tumor tissue. While the normal tissues are somewhat damaged, the destructive effect on the tumor tissue can be reached at a stage in which the normal tissues will still recover. At the present time, disease is commonly treated to the extent of producing a second degree radiodermatitis, or in other words, bleb formation with complete desquamation of the surface skin, yet, in spite of this, the skin may recover completely so that one can scarcely see the radiation effects. In this connection, when radium is used, and one removes all of the alpha rays, all of the beta rays, and about 16 per cent of the gamma rays, leaving only the more penetrating type of gamma rays by filtering the radium through 2 mm. of platinum, one can sometimes produce a well-marked radiodermatitis, and still have the hair grow afterwards.

Besides the increase in the penetrative quality of roentgen rays, apparatus has been developed which will permit an increase in quantity of rays to be given within any given period of time. In other words, in early work, one utilized commonly 1 to 5 ma. of current. Now, with the heavier equipment, it is possible to use from 6 to 30 ma. This serves to reduce the time used in treatment. Such reduction in time may or may not have advantages. Holfelder and Holthusen are both of the opinion that prolonged irradiation with even 0.5 ma. is better for the reduction of the tumor than is the large volume irradiation given in a short time. They believe that they have proved a definitely superior clinical result from small quantity of irradiation over a long time. Such prolonged irradiation, however, does increase the expenses of treatment, for it requires not only prolonged use of the apparatus, but prolonged services of the physicians and the technicians.

Another improvement in x-ray equipment that has been made during the past five years, but especially, during the past year, is the shock-proof developments. At present, many of our high voltage equipments are so protected by insulating material of one kind or another, that the patient or physician can come in direct contact with the equipment without getting any shock. There have also been improvements in protection from any stray irradiation coming from the equipment. All of these various improvements, of course, add considerably to the expense of equipment, and consequently, to the expenses of treatment to the patient.

Radium equipment. Radium equipment has likewise been improved. These improvements have consisted especially of increased quantity of radium available in the hands of various radiotherapists. In the effort to utilize the gamma rays from radium in the manner somewhat similar to the roentgen rays, as much as 4 or 5 grams of radium are put up in what is known as a "radium bomb." This consists of a lead chamber whose walls have the equivalent opacity corresponding to about 5 cm. of lead. The radium is then placed in these bombs or guns, and the rays are directed into the tumor tissue from a distance of usually 10 cm. According to the physicists' measurements, this does not produce a penetrating ray much greater than the higher voltage roentgen

rays used at a distance of 50 cm., but because of the higher filtration permitted, the biological results are claimed to be improved. The expense involved, however, is very great, and these equipments usually demand 24 hour service. They are only practical in very large institutions, and unless a radiological expert is in constant attendance, so as to direct the rays to the best advantage according to the location of the disease, the results are not likely to be appreciably improved.

Surface irradiation with gamma rays from radium seems to be on the increase because of the results that can be obtained, often without producing any permanent damage to the normal tissue. The glass seeds originally used for introduction into tumor areas have been almost abandoned in favor of a more dense walled seed, so that it is common now to use gold or platinum for the walls of these seeds, and there is an increasing tendency to introduce radium needles into the tumor tissue. These later day needles are of lower rate in content, usually from 1 to 3 milligrams or millicuries of radon and applied in needles with walls 0.5 or 0.6 thickness of iridio-platinum, and the needles vary in length from 1.5 to 6 centimeters. These needles are now inserted particularly in breast cases, and allowed to remain in place from 4 to 8 days, depending upon how much additional surface irradiation is used. The advantages of this highly filtered low-quantity irradiation from a clinical standpoint is due to the fact that the radium works continuously over a long period, and in that way, destroys the cancer cells during the stage of division at which time they are the most sensitive. They have been used particularly in breast cancer, mouth cancer, and at times, in recurring uterine cancer.

2. IMPROVEMENTS IN TECHNIC

The improvements in technic are based upon an increased knowledge of the biological effects of the rays. This emphasises the advantages of keeping up a more or less continuous irradiation over a period of three to six weeks with daily treatment or treatment twice daily when the roentgen rays are used, and with more or less continuous radiation when radium is used. Generally speaking, it has been found that one must deliver into the

tumor tissue, a total of from six to twelve erythema doses, and since a single erythema dose will produce redness of the skin, three or four erythema doses given at once will produce destruction of the skin and some of the deeper tissues. Therefore, the difficulty of delivering six to twelve erythema doses into the tumor tissue can easily be appreciated. This means in the more technical terms, a delivery of from 3,500 to at least 10,000 units. This requires skill in cross-firing, and skill in evading the essential organs such as the heart, lung tissue, the liver, spleen and the aorta. It requires skill in the matter of spacing the dosage, so as to destroy the tumor but not to do any harm to normal tissue. Technical difficulties have been greatly improved by the assistance of the physicists in showing how to determine depth doses, and how to measure in great detail the exact dosage delivered to the tumor, and to the patient as a whole.

The measurement of dosage has been one of the great problems ever since beginning the use of the roentgen rays. The Sabaraud and Noirepastiles, the Holzknecht radiometer, the Kienbök photographic method, have all served a useful purpose. Then for many years, the indirect method of measurement was depended upon, utilizing the measurement of time, distance, voltage, and milliamperage, according to the relative values, which has served very well, and which is still most valuable, but during the past 15 years, and especially during the past eight years, some form of ionometric measurement has been used to a great extent. This is basically dependent upon the measurement of the ionization of the air in the beam of radiation. This has finally led to the development and adoption of the International Unit of Quantity of X-radiation called the "roentgen," and designated "r." The International Unit of X-radiation is the quantity which, when the secondary electrons are fully utilized and the wall effect of the chamber is avoided, produces in one cubic centimetre of atmospheric air at 0°C. and 76 cm. mercury pressure, such a degree of conductivity that one electrostatic unit of charge is measured at saturation current.

By various instruments and procedures, and by utilizing the ionometric method of measurements of radiation, study has been

made of the quality of radiation, the depth dose, and the distribution of the radiation within the tissues. This has permitted exact experimental work on various biological objects.

An improvement in technic that has served well, and has given most decided improvements in end results has been the prolonged irradiation, either by the more or less constant application of radium, or by repeated fractional dosage delivered in such a manner as to destroy the tumor cells during the process of division when they are most sensitive to irradiation. Some of the older radiologists have utilized these principles during the past 35 years, but the development of the saturation method, originally suggested by Kingery, and further developed by myself, together with the development of the technic recommended by Coutard, has taught that by careful management of dosage, time and intervals, one is enabled to distribute into the tumor tissue with as much protection as possible of the normal tissue, from 6 to 10 erythema doses or from 3,600 to at least 10,000 r, and by these procedures, patients have recovered who were formerly considered hopeless. Furthermore, by these procedures, one has been able to overcome the growth of tumors that have been in the past considered radio-resistant by the pathologists. As a result of experience, but particularly, as a result of the teachings of Coutard, it has been learned that when one uses highly filtered radium and x-rays, that it is entirely possible to carry the irradiation to the point of a second degree dermatitis, and yet, have the normal tissues recover, resulting in an increased number of cures.

As a result, the field of irradiation has greatly increased, and Cutler[1] has recently stated:

> It cannot be overemphasized that the pathologist who undertakes to express an opinion on the radiosensitivity of a tumor is assuming a grave responsibility, because the surgeon who may not be completely familiar with these matters frequently bases important decisions of treatment on such information.

It is not likely that one will be able to establish a standard technic for the treatment of malignant disease until malignant disease can be made to grow according to some standard. It is better known by pathologists than by the clinical radiologists

that no two cancers are alike. They vary in the rate of growth, in the location, the extent of the disease, the character of the tumor, the resistance of the surrounding tissues, and are probably even influenced by the body chemistry. The radiologist, therefore, who has the greatest knowledge concerning the general condition of the patient, the type of tumor, distribution of the disease, and the likely areas of extension, and who, at the same time, has the most technical knowledge in the application of the principles of radiology, will obtain the best results. The results of the work of pathologists depend upon knowledge and skill and not upon instruments or the technicians who attend to some of the details; the results of surgery depend primarily upon the judgment and skill of the surgeon and not merely upon the instruments which he possesses; and likewise, radium and x-rays are only instruments in the hands of the radiologist, and the results depend upon his skill and judgment.

3. IMPROVEMENTS IN KNOWLEDGE CONCERNING SELECTED TYPES OF CASES

Ewing has taught us much with regard to the variations in the radiosensitivity of tumors of various types and locations. Broders was probably the first to classify tumors in grades of I, II, III and IV, according to their radiosensitivity or according to their microscopic appearance and degree of rapid dissemination. It so happens that grade I is least sensitive to irradiation, and is likewise less likely to lead to rapid dissemination, and therefore, the most satisfactory for operation, but it seems that Grade I represents a relatively small percentage of malignant tumors. Grade III and IV, on the other hand, are radiosensitive, but disseminate very early and very rapidly, and recur commonly after operation. While it is true that these higher grades are more sensitive to irradiation, the likelihood of rapid dissemination still makes it most desirable to treat them very thoroughly at the beginning, and as early as possible. Failures are due to the metastases.

On account of the fact that the largest number of tumors belong to grade III and IV, or certainly, beyond grade I, I have been

recommending for years that all malignant tumors from which a biopsy is to be taken should first of all have at least a full erythema dose of x-rays with the object of devitalizing the cells, so as to avoid dissemination as a result of the biopsy. Furthermore, I have been recommending that the pathological report be obtained as quickly as possible, and if the patient is then not operated upon, then certainly thorough irradiation should be started at once. By following this procedure, I have never observed any disadvantage of a biopsy. Routinely, biopsies are taken in all cases where the disease has broken through the skin or mucous membrane, and biopsies are requested in every other case when practical. The needle biopsy seems to be a very definite advance, and of especial value in radiology. Unfortunately, most surgeons, radiologists and pathologists have not mastered the technic necessary to obtain satisfactory results. Carrying out the recommendation which I have been making for years whenever I am dealing with a uterine lesion of doubtful nature, it has been my practice to do a dilatation and curettement, and through the co-operation of my associated pathologists, I have been able to obtain a report on fixed specimens within 24 hours. In practically all cases of this character that come to the radiologists, there is associated uterine hemorrhage, and therefore, immediately, following the dilatation and curettement, it has been my practice to insert radium in the full length of the uterine cavity during this period of 24 hours. This will do no harm, and will serve to arrest the growth which might otherwise be stimulated due to this traumatism. If the disease is then malignant, the radium can be left in place long enough to accomplish the desired results.

As a result of these various studies, it has been found that certain types of cancer are totally unsuitable for operation. One of these types is the malignant lymphangitis which spreads rapidly through or beneath the skin and gives an appearance resembling somewhat erysipelas. For this reason, it has been called "erysipelas carcinomatosum" by Küttner, and "carcinoma erysipelatodes acutum" by Rasch, while Unna has called this condition "carcinomatösem Lymphbahninfarkt." The great importance of this type of disease in the field of radiology is the fact that it may

simulate a radiodermatitis. The only control that one has of this disease is by irradiation, and therefore, if the proper treatment is withheld because of the diagnosis of radiodermatitis, such patients will receive no assistance and will pass on to death.

I have been especially interested in this because in several cases, when this disease followed some form of irradiation, it has been interpreted as a radiodermatitis.* This type of disease has a number of variations, and occurs independent of irradiation, but the type that particularly concerns me is that which produces a general deep redness of the skin, which may grow in areas that have been previously treated by irradiation but not treated sufficiently to destroy all of the cancer cells, and suggests to the inexperienced a radiodermatitis. It can be distinguished, however, from radiodermatitis first, because it extends definitely beyond the areas that have been treated by the rays; second, it has an irregular border while our radiation treatment areas are usually along even lines; third, the disease has a more blotchy appearance than one gets in a radiodermatitis; fourth, sooner or later, definite nodules develop, and fifth, this disease terminates in localized ulcers instead of desquamation of the surface as one finds in radiodermatitis.

4. IMPROVEMENTS IN RESULTS FOLLOWING TREATMENT OF THE X-RAYS AND RADIUM

There are seven great groups of malignant disease in which treatment by irradiation has produced rather striking results, and in which the rays are being depended upon more and more as a primary form of treatment. These are:

(1) *Cancer of the skin.* Cancer of the skin can be treated successfully by irradiation, or especially when combined with electrocoagulation in practically

* I am demonstrating to you particularly one case that shows this striking resemblance very clearly, and yet, it is definitely a malignant lymphangitis, and though very extensive, has responded to irradiation. In this instance, I have been fortunate through the splendid coöperation of Dr. Eugene Case to get specimens both before treatment and after treatment, for which I am calling upon him or Dr. Stanley Reimann to demonstrate to you in discussion of this subject.

all cases. This is a real advance, for 35 years ago it was a triumph to get a cancer of the skin well.

(2) *Cancer of the lip* can be cured in 98 per cent when the primary lesion is treated by electrocoagulation following biopsy, or by very thorough local application of radium, or x-rays, and provided the regional lymphatics are thoroughly treated by high voltage x-rays.

(3) *Cancer of the mouth*, in my opinion, should give good results in about 75 per cent of the cases providing it is treated skillfully with highly filtered radium inside, and externally, or with radium applications or interstitial radium inside combined with highly filtered high voltage x-rays externally. As a matter of fact, only about 30 per cent of the mouth cases as they now come, and as they are now treated, are being cured at the present time. This is due to late treatment or inefficient treatment. Even 30 per cent is a definite advance as compared with the results obtained when all of us were undergraduates.

(4) *Cancer of the larynx.* It is well recognized that when cancer of the larynx is strictly intrinsic, a high percentage can be gotten well by operative procedures. I am convinced, however, that the best results in extrinsic laryngeal or pharyngeal cancer can be obtained by using highly filtered radium or x-ray applications, with daily treatment, over a period of from three to six weeks. At present, only about 22 per cent of these extrinsic cases get well, but this is almost entirely a 22 per cent salvage as compared with the results obtained formerly by other methods.

(5) *Cancer of the uterus.* The results in the treatment of cancer of the uterus have improved sufficient to make irradiation the first choice. When dealing with cancer of the cervix, which is strictly confined to the cervix, the results obtained have varied from 40 to 100 per cent. Lacassagne has reported a small series of cases in which 100 per cent of five year cures was obtained in the group classed as stage I. Stage I and II combined, which embraces all of the operable cases, shows in the statistical group from 40 to 60 per cent recoveries according to various authors from radiation treatment, and there has been a definite salvage of some of the more advanced cases running as high as 20 per cent. Even carcinoma of the body of the uterus has shown approximately equal or even superior results, as compared with operation when treated thoroughly by radiation, giving from 50 to 60 per cent cures.

(6) *Cancer of the breast.* Cancer of the breast, when treated by the combination of surface and the modern interstitial radiation using radium needles from 4 to 6 cm. in length, and with the radium filtered through 0.5 or 0.6 irridioplatinum, has given approximately 46 per cent five year cures. This is approximately equal to the results obtained by operation and irradiation combined.

(7) *Carcinoma of the bladder.* More recently, carcinoma of the bladder is being diagnosed successfully, and is being treated successfully by irradiation. In this field, I have been especially interested, and it is my opinion, which is not supported by statistics, but by a clinical impression based upon the response that I am obtaining, that one should get about half of the patients well as they now come for treatment.

Malignant disease can in many instances be retarded or influenced in other parts of the body, but the deeper the disease and the more closely associated with vital organs, which are affected by irradiation, the more difficult it is to treat them in this manner. One must therefore still depend upon surgery in most visceral cases as the bulwark in the fight against malignant disease. However, with present knowledge and present technic, the importance of radiotherapy in the treatment of malignant disease is shown by the records of St. Georg Hospital in Hamburg, where 1559 cases of malignant disease were treated between 1931 and 1933. Of these, 60 per cent were treated by radiotherapy, 23.3 per cent were treated by surgery, of which 12.4 per cent also received radiotherapy.[2]

This hasty review of the subject is by no means complete, but it is intended to give to the busy clinical pathologists some general idea of the progress that is being made in clinical radiology.

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CYTOLOGICAL STUDIES OF MALIGNANT TUMORS*

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Since Virchow's formulation of the cellular theory of cancer, numerous attempts have been made to discover characteristic stigmata of cancer cells. Certain changes observed in the nucleus of malignant cells have been at all times of primary scientific interest, and Fischer Wasel still believes that future research may establish cancer as a disease of the nucleus. In his recent review of the histological conception of malignancy, Borst[2] states emphatically that definite morphological characteristics of malignant cells do not exist, and that at present the autodestructive type of growth must be regarded as the most important, if not the only, histological proof of cancer. He admits, however, that certain cytological changes may be helpful for the diagnosis of a malignant tumor although the absence of these changes does not exclude the presence of cancer. Among these he mentions variations in size and shape of the nucleus as brought out by the studies of Heiberg and his school, and atypical pictures of mitoses as emphasized by von Hansemann and others. He deplores in this critical review the lack of systematic investigations and of sufficient comparative studies of non-malignant lesions necessary to give such observations a better foundation.

Changes in the nucleolus of cancer cells, the object of this presentation, are described as early as 1896 by Pianese, and Quensel[22] in 1918 recommended the study of the nucleolus for the diagnosis of malignant cells in the sediment of urine. In his morphological study of bladder tumors, Stenius[27] describes the nucleoli of malignant cells as oval and irregular in shape, with a

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diameter of 3 to 4 microns, in contrast to the round and small nucleoli in benign papillomas with a diameter of 1 to 2 microns. Castren,[4] studying the connective tissue tumors with special reference to the fibromas and sarcomas, observes that the nucleoli in the cells of progressive type are much larger than in the cells of regressive type, the difference in diameter being often as large as 5 microns. He emphasizes, however, that not all types of sarcoma are characterized by large nucleoli and he could observe some very malignant round cell sarcomas which did not show cells of progressive type. He concludes that the number of large nucleoli in a connective tissue tumor can not be taken as an estimate of the degree of malignancy. Extensive variations in the size and number of the nucleolus are emphasized by Saxen[25] in his study of malignant papillomas and carcinomas of the nasal cavity and the bordering sinuses. He stresses especially the appearance of large nucleoli measuring 4.5 to 6 microns in diameter in small nuclei. One of the most intensive discussions of this problem in continental literature can be found in Quensel's[23] monograph on his cytological examination of serous exudates. Using a specially prepared mixture of methylene blue and Sudan red, he observed a "peculiar change of the nucleolus" in malignant cells, showing increase in size and number and marked irregularity in shape; diameters up to 9 microns were reported by Quensel as not unusual, and he often counted from 9 to 14 nucleoli in the nucleus of a malignant cell. The relation of nucleolus to nucleus in malignant cells varied from 0.20 to 0.60 against 0.14 to 0.16 in normal endothelial cells of serous membranes. The shape of the malignant nucleolus was found to be usually oval or polygonal, rarely round as in normal cells. Citing analogous observations in cell cultures (Chlopin, Maximow), Quensel concludes that this morphological change in the nucleolus signifies a profound alteration in the metabolism of the nuclei of malignant cells. According to the recent work of Saguchi,[24] the nucleolus is not a constant formation but changes continuously during the life cycle of the cell and must be regarded as an important reserve depot for various chemical build stones of the nucleus.

An important contribution to this puzzling problem of cellular

morphology is the work of MacCarty[16] who, made the statement that:

> Both reparative regenerative and malignant regenerative cells possess one or more nucleoli, but, as a rule, those of the malignant cells are much larger in proportion to the nucleus than those of the reparative.

In pursuance of his research, MacCarty, with Haumeder and Berkson,[17] observed that the mean areas of the nucleoli in malignant cells increase more than the mean areas of the nuclei when compared with the areas of nuclei and nucleoli of non-malignant cells. Therefore, the nuclear-nucleolar ratio was found to be lower in malignant cells than in benign cells. MacCarty and Haumeder[18] published their most recent investigations, in which only unfixed material was used and which confirmed their previous observations. Seven hundred cells from 65 malignant tumors gave a nuclear-nucleolar ratio between 5 to 1 and 14 to 1; 360 cells from 22 non-malignant lesions showed a nuclear-nucleolar ratio between 13 to 1 and 25 to 1. There was an overlapping of values in 20.1 per cent of the examined cells. In the conclusion the claim is made by the authors that malignant cells appear to have at least one characteristic sign, which they recommend for use in the differential diagnosis of cancer. They also stress the necessity "for histopathologists becoming fresh tissue cytologists," as the above described changes are outstanding only in slides made from unfixed tissues.

Although conservative investigators like Fischer Wasels[6] and Borst still hesitate to draw any conclusions from the work of Quensel and MacCarty, there are numerous authors who have begun to take notice of this observation. Haumeder[11] states that a large nucleolus is so characteristic for malignant cells that it is "surprising" that this phenomenon has not been stressed before as it is much more noticeable than the increase in the size of the nucleus. Only the fact that most of histological methods stain the chromatin substance of the nucleus rather than the nucleolar substance, and the neglect to examine slides more frequently under oil immersion, can explain this oversight. Poole and Dunlop[21] mention the large nucleolus as a valuable help to recognize

cancer cells in the peripheric blood stream and to differentiate them from large monocytes. Karp's[14] cytological measurements confirm the observation of the large nucleolus in malignant cells, and Zadek[29] very emphatically states that an increased number of large and polygonal nucleoli in small nuclei must be looked upon as the most important characteristic sign of tumor cells. Since pictures of atypical mitosis can not be regarded any more as specific for malignant cells (Andres[1]) and in the light of the recent biometric research of Wermel and Scherschulskaja[28] as well as of Ludford's[15] studies on the distribution of chromatin in cancer cells, the few accepted characteristics of malignant cells (Borst) have lost their value, it will be necessary to review our previous histological conception of the cancer cell. The observation concerning the nucleoli of malignant cells which has not been refuted so far certainly deserves the utmost scientific interest and calls for confirmation and further systematic investigation.

In undertaking the present study, we were faced with two different problems: to confirm the startling results of MacCarty and his coworkers and to explore the possibility of introducing this observation as a new and practical method of tumor diagnosis. MacCarty recommends measurement of the mean area of each nucleus and nucleolus with the aid of a camera lucida and a planimeter, and his published data represent the compiled values of groups of ten cells. He selects only nuclei with a single nucleolus, and his investigation shows an overlapping of values in 20.1 per cent of the examined cells. His average values, however, compiled from several hundred cells, demonstrate much more strikingly the difference between benign and malignant lesions, which can be explained according to Castren by the fact that in a large number of cancer cells a greater number of proliferative cells with giant nucleoli will be encountered. To compile the values of a greater number of cells should therefore reduce the percentage of overlapping figures for malignant and benign lesions, and make the method more accurate for diagnostic purposes. Another factor to be considered in any routine laboratory method is the time period necessary for its execution. The manipulation with the planimeter, as suggested by MacCarty, requires

expert training and time taking mathematical calculations, and cannot be introduced into the routine laboratory technic. After many trials we decided upon the following method, which we will describe in detail in order to obviate repetition.

METHOD

The material studied in our investigation comprised fifty malignant tumors and fifty non-malignant tissues, the latter serving as controls. The majority of the malignant tumors examined belonged to the group of carcinomas; the benign specimens consisted of tissues taken from normal organs (16), of tissues which were the site of inflammatory or degenerative processes (23), and of tissues taken from benign tumors (11). Slides were prepared for the microscopic examination from tissues fixed in formalin and embedded in paraffin, from frozen sections, and from cell suspensions. The slides obtained from the fixed tissues were stained with hematoxylin eosin; the frozen sections and the smears prepared from the cell suspensions were stained with a highly diluted aqueous solution of toluidin blue (1:10,000) according to the method described by the authors in a previous publication (von Haam and Alexander). The hypotonic character of this staining solution causes the chromatin substance of the unfixed nuclei to swell while the more resistant nucleoli retain their outline and become prominent (Hertwig). After a counter-stain with methyl green the nucleoli appear as deep purple or pink globoid bodies in the homogeneously green-stained nuclear substance. Those slides prepared after the various methods were projected through an oil immersion objective and a prysmatic projection eye piece upon a narrow strip of translucent waxed paper, where the outlines of the nuclei and nucleoli were traced with India ink. Realizing the great influence of the selection of the cells to be measured upon the value compiled from each slide, the following method was adopted and carried out identically in all our examinations. From each microscopic field the four nuclei with the approximately greatest amount of nucleolar substance were chosen to be drawn, regardless of the number of nucleoli in each nucleus. Malignant cells were found to be characterized by a large number of nucleoli, as observed by other authors. Twenty-five microscopic fields were examined in each slide and a total number of one hundred cells was studied. The tracings on the wax paper were then enlarged by means of a Leica enlarging apparatus (Leitz) and projected upon white cardboard (commercial Tag board), where the traced outlines of the nuclei and nucleoli were cut out with a sharp knife. By means of the known factors of magnification and enlargement, the specific weight of the cardboard and the weight of the cut out figures, the mean area of the nuclei and nucleoli was then estimated in square microns according to the formula:

$$\text{Mean area} = \text{Weight} \times 73.4 \text{ (square microns)}$$

TABLE 1

MALIGNANT TUMORS

CASE	SEX	AGE	SPECIMEN	DIAGNOSIS	NUCLEAR-NUCLEOLAR RATIO FOR 100 CELLS	REMARKS
1	M.	60	Finger	Squamous cell carcinoma	12.2	Paraffin section
2	M.	63	Skin	Spindle cell sarcoma	14.4	Cell suspension
3	M.	45	Leg	Squamous cell carcinoma	13.8	Paraffin section
4	F.	60	Breast	Medullary carcinoma	12.1	Frozen section
5	M.	60	Finger	Squamous cell carcinoma	15.4	Paraffin section
6	F.	44	Cervix	Squamous cell carcinoma	12.4	Paraffin section
7	F.	49	Cervix	Squamous cell carcinoma	15.6	Paraffin section
8	F.	36	Breast	Medullary carcinoma	14.8	Cell suspension
9	F.	52	Scalp	Basal cell carcinoma	15.2	Paraffin section
10	M.	64	Cecum	Adenocarcinoma	14.5	Paraffin section
11	F.	47	Sigmoid	Adenocarcinoma	13.6	Cell suspension
12	M.	52	Palate	Squamous cell carcinoma	12.2	Frozen section
13	F.	52	Breast	Medullary carcinoma	13.3	Cell suspension
14	F.	37	Breast	Scirrhus carcinoma	14.7	Cell suspension
15	M.	70	Hand	Squamous cell carcinoma	11.4	Frozen section
16	M.	42	Lip	Squamous cell carcinoma	11.8	Cell suspension
17	F.	80	Skin	Squamous cell carcinoma	16.2	Paraffin section
18	M.	70	Skin	Spindle cell sarcoma	15.5	Paraffin section
19	F.	34	Cervix	Squamous cell carcinoma	15.6	Paraffin section
20	F.	68	Breast	Medullary carcinoma	12.0	Frozen section
21	M.	54	Penis	Squamous cell carcinoma	15.5	Paraffin section
22	M.	60	Eye	Mycosis fungoides	15.8	Paraffin section
23	M.	61	Lymph gland	Squamous cell carcinoma	8.1	Frozen section
24	F.	32	Breast	Medullary carcinoma	12.0	Frozen section
25	M.	35	Testis	Embryonal sarcoma	14.5	Paraffin section
26	M.	49	Liver	Bile duct carcinoma	14.4	Paraffin section
27	M.	30	Hand	Squamous cell carcinoma	16.1	Frozen section
28	F.	17	Breast	Medullary carcinoma	11.1	Cell suspension
29	F.	55	Cervix	Squamous cell carcinoma	11.1	Cell suspension
30	F.	72	Breast	Scirrhus carcinoma	9.1	Cell suspension
31	M.	63	Tongue	Squamous cell carcinoma	14.0	Paraffin section
32	F.	36	Cervix	Squamous cell carcinoma	13.7	Paraffin section
33	M.	65	Lung	Bronchogenic carcinoma	11.8	Cell suspension
34	M.	70	Hand	Squamous cell carcinoma	9.8	Cell suspension
35	M.	60	Tongue	Squamous cell carcinoma	11.1	Paraffin section
36	F.	45	Breast	Medullary carcinoma	11.6	Paraffin section
37	F.	56	Breast	Medullary carcinoma	13.0	Paraffin section
38	M.	65	Bladder	Papillary carcinoma	12.9	Cell suspension

TABLE 1—*Concluded*

CASE	SEX	AGE	SPECIMEN	DIAGNOSIS	NUCLEAR-NUCLEOLAR RATIO FOR 100 CELLS	REMARKS
39	F.	21	Lung	Chorionepithelioma	13.7	Cell suspension
40	F.	60	Breast	Scirrhus carcinoma	13.4	Paraffin section
41	M.	70	Hand	Squamous cell carcinoma	12.6	Paraffin section
42	F.	62	Breast	Paget's disease	12.0	Paraffin section
43	M.	35	Breast	Medullary carcinoma	10.5	Frozen section
44	F.	36	Breast	Medullary carcinoma	8.6	Frozen section
45	M.	66	Stomach	Scirrhus carcinoma	13.2	Frozen section
46	M.	52	Stomach	Adenocarcinoma	15.1	Frozen section
47	M.	48	Lymph gland	Adenocarcinoma	13.4	Cell suspension
48	M.	61	Lymph gland	Squamous cell carcinoma	12.5	Paraffin section
49	F.	35	Breast	Medullary carcinoma	14.3	Paraffin section
50	M.	78	Stomach	Medullary carcinoma	11.2	Cell suspension

Drawings of known microscopic areas such as the squares of a blood counting chamber (Thoma-Zeiss) showed that the error caused by incorrect or careless drawing, thickness of the tracing lines and inexact cutting, could be kept, after some practice, well below plus or minus 5 per cent.

From the mean areas of the nuclei and nucleoli, the relation factor for one hundred cells was then determined in each slide. A total number of 10,000 cells was examined in our investigation; 5,000 were cells from malignant tumors and 5,000 were cells from benign lesions. The advantage of our method is that it is comparatively simple and does not take much time. The pathologist has to select the cells and trace the outlines of the nuclei and nucleoli upon the narrow strips of waxed paper, a task which consumes, after some practice, one hour for hundred cells. The remaining procedure can then be accomplished in about two hours by any conscientious and practiced assistant.

RESULTS

The results of our investigations are compiled in the tables, which give the nuclear-nucleolar quotient for one hundred cells of each slide examined. Table 1 lists the malignant tumors with the values for the nuclear-nucleolar ratio varying from 8.1 to 16.2, table 2, the benign lesions with a nuclear-nucleolar quotient between 9.1 and 29.4. Only two of the fifty examined malignant tumors show a nuclear-nucleolar ratio higher than 16 to 1, both

TABLE 2

BENIGN LESIONS

CASE	SEX	AGE	SPECIMEN	DIAGNOSIS	NUCLEAR-NUCLEOLAR RATIO FOR 100 CELLS	REMARKS
1	M.	78	Kidney	Normal tissue	18.8	Cell suspension
2	M.	61	Liver	Normal tissue	23.0	Cell suspension
3	M.	19	Skin	Sporotrichosis	19.6	Paraffin section
4	F.	20	Rectum	Polyp	26.9	Paraffin section
5	M.	35	Skin	Eczema	24.1	Paraffin section
6	M.	52	Stomach	Normal tissue	16.9	Cell suspension
7	M.	19	Kidney	Normal tissue	20.1	Frozen section
8	F.	9	Spleen	Lymphatic leukemia	21.8	Cell suspension
9	M.	16	Skin	Tertiary lues	29.4	Paraffin section
10	F.	60	Skin	Eczema	25.1	Paraffin section
11	F.	22	Breast	Fibroadenoma	17.7	Cell suspension
12	F.	18	Cervix	Cystic cervicitis	26.9	Paraffin section
13	F.	28	Pancreas	Normal tissue	21.0	Cell suspension
14	F.	18	Kidney	Normal tissue	17.1	Cell suspension
15	F.	36	Breast	Cystic adenoma	22.5	Cell suspension
16	F.	56	Parotis gland	Mixed tumor	16.5	Frozen section
17	M.	18	Appendix	Acute inflammation	17.8	Paraffin section
18	F.	29	Vagina	Secondary lues	22.0	Paraffin section
19	F.	32	Uterus	Endometritis	17.8	Cell suspension
20	F.	37	Vulva	Syphilis	16.7	Paraffin section
21	M.	49	Skin	Lupus	19.4	Paraffin section
22	F.	34	Uterus	Fibroid	16.5	Frozen section
23	F.	46	Uterus	Endometritis	15.8	Cell suspension
24	M.	28	Lip	Chancre	21.7	Paraffin section
25	F.	47	Skin	Verruca	22.7	Paraffin section
26	F.	24	Breast	Adenofibroma	23.7	Frozen section
27	F.	47	Uterus	Fibroid	21.2	Paraffin section
28	F.	28	Cervix	Granuloma	24.7	Paraffin section
29	F.	29	Ovary	Corpus luteum	9.7	Cell suspension
30	M.	33	Skin	Eczema	17.6	Paraffin section
31	F.	29	Skin	Pityriasis rosea	18.0	Paraffin section
32	F.	48	Adrenal	Normal tissue	16.2	Cell suspension
33	F.	48	Kidney	Nephrosis	14.6	Cell suspension
34	F.	22	Uterus	Endometritis	21.1	Cell suspension
35	F.	38	Breast	Adenofibroma	16.7	Frozen section
36	F.	45	Cervix	Cervicitis	23.6	Paraffin section
37	F.	40	Cervix	Cervicitis	24.5	Paraffin section
38	M.	41	Stomach	Peptic ulcer	22.0	Frozen section
39	F.	29	Ovary	Follicular cyst	24.8	Cell suspension

TABLE 2—*Concluded*

CASE	SEX	AGE	SPECIMEN	DIAGNOSIS	NUCLEAR-NUCLEOLAR RATIO FOR 100 CELLS	REMARKS
40	F.	31	Ovary	Corpus luteum	9.1	Cell suspension
41	F.	46	Breast	Fibroadenoma	16.0	Cell suspension
42	F.	33	Skin	Chronic mycosis	20.9	Paraffin section
43	M.	nb	Kidney	Normal tissue	23.8	Cell suspension
44	M.	nb	Adrenal	Normal tissue	16.6	Cell suspension
45	F.	45	Breast	Fibroadenoma	18.5	Frozen section
46	M.	55	Skin	Luetic ulcer	15.8	Paraffin section
47	M.	nb	Liver	Normal tissue	23.4	Cell suspension
48	F.	18	Ovary	Corpus luteum	14.7	Paraffin section
49	M.	nb	Brain	Normal tissue	22.4	Cell suspension
50	F.	26	Uterus	Endometrium	25.0	Cell suspension

of these cases being a slow-growing squamous cell carcinoma of the skin without metastasis. Forty-six of the benign lesions which served as controls gave a nuclear-nucleolar ratio higher than 16 to 1; four specimens (29, 33, 40 and 48) showed values below this margin. In cases 29, 40 and 48 the object of our biometric investigation has been the cells of a corpus luteum of the ovary, and it is of interest that the nuclear-nucleolar ratio in all three instances was found to be low, resembling values found in malignant tumors. In case 33 the tubular epithelium of a nephrotic kidney was examined.

A graphic demonstration of the difference in the nuclear-nucleolar ratio between benign and malignant tissues is shown in figure 1. The malignant tumors are subdivided into the groups of clinically less malignant and highly malignant tumors. The benign control specimens comprise the groups of normal tissues, inflammatory lesions and benign tumors. The horizontal line makes the division between the nuclear-nucleolar ratio of the benign and malignant lesions. If we consider the corpus luteum cells (cases 29, 40 and 48) as an exceptional group, excluding it from the present analysis, we observe only one benign lesion showing a nuclear-nucleolar ratio below 16 to 1, and two malignant lesions showing a nuclear-nucleolar ratio above 16 to 1.

The influence of fixation upon the nuclear-nucleolar ratio is demonstrated in figure 2. A comparison between forty-five fixed specimens and fifty-five unfixed specimens examined partly after the preparation of frozen sections (18) or of cell suspensions (37) shows that the difference between the malignant and benign lesions is equally distinct for fixed as for unfixed tissues. That the nuclear-nucleolar ratio of unfixed tissues gives slightly lower values can be explained by the fact that the vital stain used in

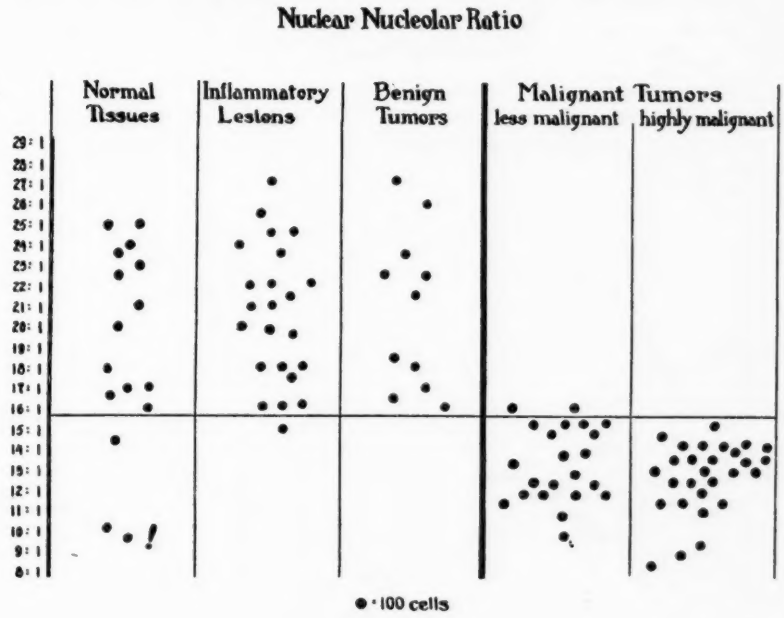

FIG. 1

the frozen sections and cell smears is specific for the nucleolar substance, while the hematoxylin used in the paraffin sections makes the chromatin substance more prominent.

In table 3 the average nuclear-nucleolar ratio for the various cell groups is as follows: 5,000 cells examined in benign lesions show an average ratio of 20.15 to 1, with twenty-five of the specimens giving higher and twenty-five of the specimens giving lower values. The average ratio of the nucleus to the nucleolus in 5,000 malignant cells is 13.01, with twenty-four of the examined

tumors showing a lower and twenty-six of the specimens showing a higher value. The figures compiled for the groups of slides prepared from paraffin sections, frozen sections and cell suspensions differ but little from each other, the paraffin sections giving a slightly higher nuclear-nucleolar quotient.

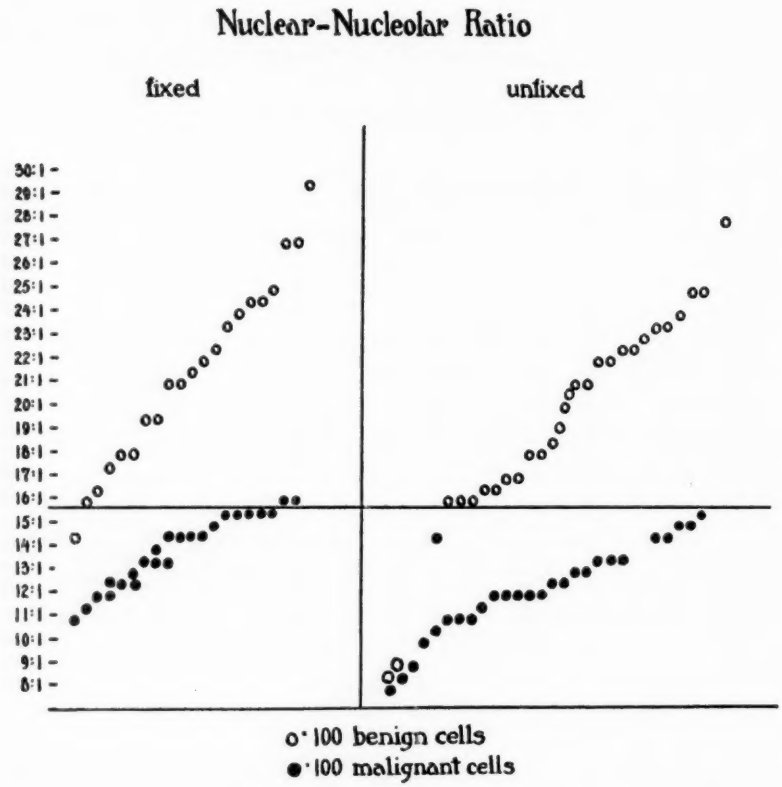

FIG. 2

Tables 4 and 5 show the mean areas of the nuclei and nucleoli for 100 cells of each specimen. The compiled nuclear areas measure from 27.8 to 118.5 square microns in the group of malignant tumors and from 20.6 to 96.7 square microns for the benign lesions. The compiled values for the nucleolar areas vary from 1.83 to 8.71 square microns for the malignant tumors and from

TABLE 3

Nuclear-nucleolar ratio. Average values (10,000 cells)

Benign lesions	*20.15*:1
Paraffin sections (2100 cells)	21.59:1
Frozen sections (700 cells)	20.79:1
Cell smears (2200 cells)	18.56:1
Malignant lesions	*13.01*:1
Paraffin sections (2400 cells)	13.86:1
Frozen sections (1100 cells)	11.76:1
Cell smears (1500 cells)	12.70:1

TABLE 4

MALIGNANT LESIONS

CASE	NUCLEAR AND NUCLEOLAR AREAS OF 100 CELLS		CASE	NUCLEAR AND NUCLEOLAR AREAS OF 100 CELLS	
	Nucleus	Nucleolus		Nucleus	Nucleolus
	sq. μ	*sq. μ*		*sq. μ*	*sq. μ*
1	46.6	3.82	26	66.0	1.62
2	51.1	3.54	27	29.6	1.83
3	64.7	4.69	28	27.8	2.50
4	60.0	4.95	29	35.2	3.07
5	75.0	4.86	30	46.5	5.11
6	52.6	4.24	31	90.9	6.49
7	55.8	3.67	32	66.7	4.87
8	39.6	2.67	33	33.4	2.82
9	32.8	2.15	34	32.9	3.35
10	46.8	3.22	35	57.8	5.20
11	118.5	8.71	36	75.1	6.47
12	35.2	2.88	37	44.4	3.41
13	64.9	4.80	38	63.6	4.92
14	111.0	7.55	39	32.4	2.37
15	39.2	3.43	40	74.1	5.53
16	50.5	4.28	41	54.7	4.34
17	70.3	4.33	42	61.7	5.14
18	57.6	3.71	43	36.7	3.42
19	59.8	3.83	44	52.3	6.07
20	51.2	3.82	45	43.5	3.29
21	55.8	3.60	46	55.7	3.69
22	32.6	2.06	47	49.5	3.70
23	57.4	7.01	48	72.3	5.78
24	34.0	2.80	49	38.7	2.70
25	65.4	4.51	50	54.6	4.87

1.03 to 6.57 square microns for the benign lesions. The corpus luteum cells (cases 29, 40 and 48) are characterized by an excessively large nucleolus, which explains the low nuclear-nucleolar ratio in those cells.

TABLE 5

BENIGN LESIONS

CASE	NUCLEAR AND NUCLEOLAR AREAS OF 100 CELLS		CASE	NUCLEAR AND NUCLEOLAR AREAS OF 100 CELLS	
	Nucleus	Nucleolus		Nucleus	Nucleolus
	sq. μ	sq. μ		sq. μ	sq. μ
1	39.3	2.15	26	51.3	2.17
2	42.9	1.87	27	65.4	3.08
3	47.4	2.42	28	68.7	2.79
4	93.9	3.46	29	30.4	3.14
5	45.8	1.90	30	65.2	3.70
6	43.5	2.57	31	66.6	3.70
7	35.6	1.77	32	46.2	2.85
8	44.0	2.02	33	48.8	3.30
9	57.3	1.95	34	31.4	1.48
10	74.0	2.95	35	38.4	2.29
11	60.9	3.44	36	59.0	2.50
12	73.8	2.74	37	53.0	2.16
13	45.1	2.14	38	64.2	2.91
14	34.2	1.48	39	44.8	1.81
15	54.2	2.40	40	36.6	4.01
16	37.4	2.27	41	27.9	1.74
17	41.0	2.30	42	52.1	2.49
18	46.7	2.10	43	32.3	1.36
19	35.9	2.02	44	27.4	2.58
20	58.8	3.52	45	30.4	1.63
21	49.5	2.55	46	57.5	3.63
22	28.9	1.03	47	41.2	1.76
23	23.2	1.46	48	96.7	6.57
24	69.1	3.18	49	59.2	2.64
25	43.7	1.92	50	20.6	1.03

A better analysis of the compiled data is permitted in figure 3, which demonstrates a much greater difference between the nucleolar areas of benign and malignant cells than between the nuclear areas of both cell groups. The graphic curves of this table show that nuclei as well as nucleoli are larger in the cells of malignant

tumors, but the increase in nucleolar substance is much more prominent, thus explaining the change in the nuclear-nucleolar ratio in malignant tumors as compared with benign lesions.

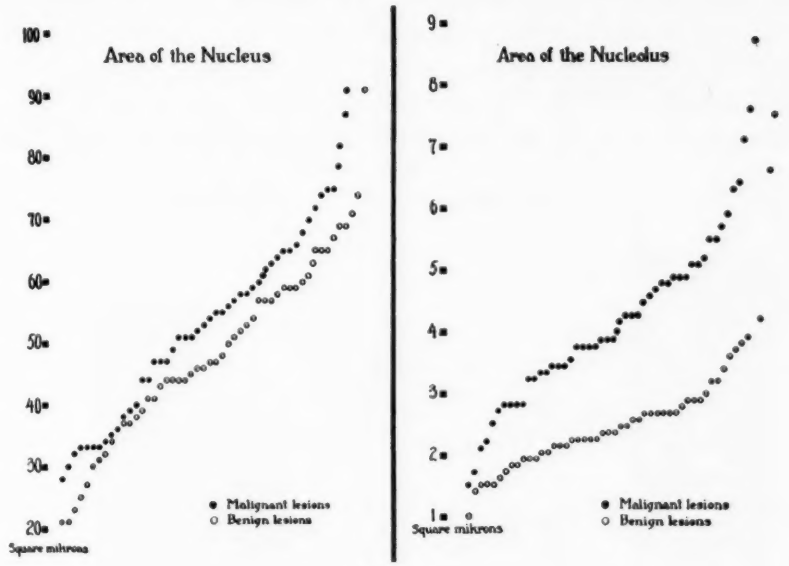

FIG. 3

DISCUSSION

The above published biometric data obtained from 10,000 cells examined in benign and malignant lesions confirm the observation of Quensel, MacCarty and others that the nucleolar substance is more abundant in the cells of malignant tumors than of benign tissues. This increase of the nucleolar substance has been found sufficiently prominent in our investigations to cause a change in the nuclear-nucleolar ratio, estimated for 100 cells in each specimen examined. Only two cases of slow-growing carcinoma of the skin without metastasis gave nuclear-nucleolar proportions as encountered in non-malignant tissues. The ratio between nucleus and nucleolus estimated for a total number of 5,000 cells from malignant tumors was about 35 per cent lower than the average ratio compiled from 5,000 cells of the control lesions (fig. 4).

Before we consider the significance of our results, it will be necessary to answer two important questions closely related to this problem: first, does every type of malignant tumor show such an abundant nucleolar substance, and, second, is a large nucleolus a characteristic of each malignant cell? Our examinations have not been sufficiently numerous to answer the first question. With the exception of two spindle-cell sarcomas, one chorion epithelioma and one hypernephroma, all of the examined fifty specimens

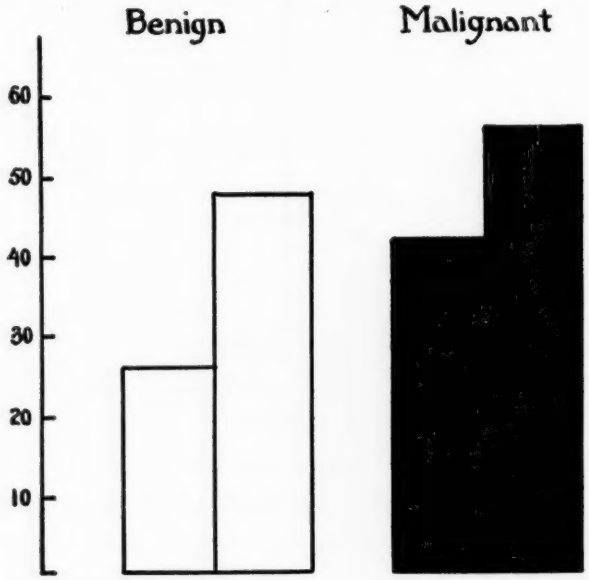

FIG. 4

belonged to the group of carcinoma. Castren's statement that the cells in round cell sarcomas do not possess large nucleoli could therefore be neither confirmed nor refuted, and further investigations will be necessary to decide this question. Of the malignant tumors examined by us, ninety-six per cent showed a nuclear-nucleolar ratio below 16 to 1, which findings are in confirmation with MacCarty's results.

The second question can be answered, according to our experience, with the statement that neither size, shape or number of the nucleoli represents any common characteristic for malignant

cells. Although it is true that the majority of the cells in malignant tumors possess large nucleoli (fig. 5), some of which are much larger than ever encountered in benign lesions, there are many cells in cancerous tissues showing small nucleoli. The number of nucleoli in the cells of malignant tumors was found usually increased, and as many as twelve nucleoli could be counted in some cells. This increase in the number of nucleoli has not been emphasized sufficiently by MacCarty, and we consider it an important factor in the change of the nuclear-nucleolar ratio. In

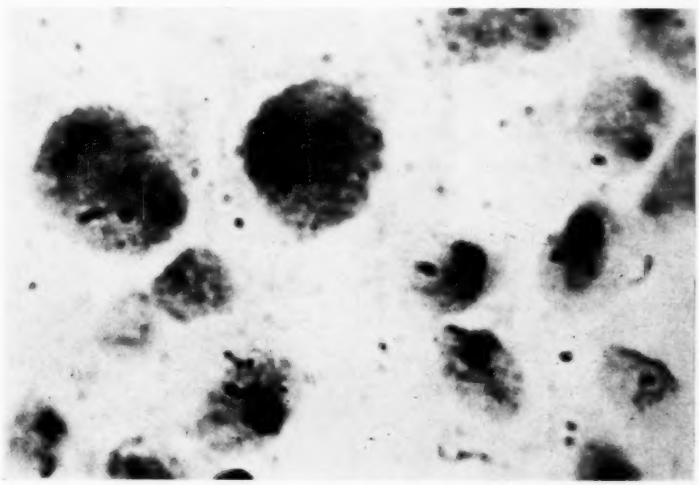

FIG. 5. NUCLEI AND NUCLEOLI FROM A CARCINOMA OF THE STOMACH
(Toluidine blue, ×1350)

benign tissues rarely more than two nucleoli are encountered in each cell. The total number of nucleoli in each cell can be better demonstrated with the toluidin stain (von Haam-Alexander), as the hemotoxylin covers many of the smaller nucleoli. Probably the most impressive difference between the nucleoli of malignant and non-malignant cells appears in the shape of those intranucleolar structures. The nucleoli of cancer cells represent all types of bizarre forms, with a great number of polygonal and bacilliform nucleoli encountered in each malignant tumor. The nucleoli of benign cells are, with rare exceptions, round or slightly oval.

Our findings concerning the influence of fixation upon the nuclear-nucleolar ratio differ from those of MacCarty, which may be explained by the modified technic. According to our results, it is not absolutely necessary for pathologists to become "fresh tissue cytologists," although the study of unfixed tissues has its above described advantages.

We are fully aware that our investigations, at the present time, do not permit any far-reaching conclusions, and the following brief consideration of the practical and scientific value of our work shall be attempted only with the purpose of stimulating further research.

The urgent need of a diagnostic method for malignant cells is an acknowledged fact. Although the perception of atypical and destructive tissue proliferation will always remain the best way of diagnosis in established cases of cancer, there are a number of occasions in which this method cannot be employed. The diagnosis of malignant cells in exudates, urine, gastric juice, or cell smears prepared from a punch biopsy must rely entirely upon the recognition of single tumor cells. Atypical pictures of mitosis are rare in cells not fixed instantaneously, and other probable signs of malignancy, as large multinucleated cells or giant vacuoles in the cell plasma, have only little diagnostic value. The possibility of using the nucleolus as a criterion in tumor diagnosis has been discussed already by MacCarty, Quensel and others. While most of the authors merely suggest using the presence of the large nucleolus only as an aid in the diagnosis, MacCarty expresses his belief that the nuclear-nucleolar ratio of cells could be made a valuable diagnostic factor in the recognition of malignancies. His complicated method requiring the manipulation of a planimeter, and the relatively high percentage of overlapping values for benign and malignant lesions seem to have thus far discouraged other investigators from taking up his suggestion. Both disadvantages have been diminished by our method, which is much simpler, and which reduces the percentage of overlapping figures through the complication of values from groups of one hundred cells instead of ten cells. As in every method dealing with average values, the precision of diagnosis will increase with the number

of cells examined, and according to our preliminary investigations, biometric measurements of one hundred cells seem to give a sufficiently accurate diagnosis of malignancy. Although this procedure does not represent an ideal solution of a cytological tumor diagnosis, we offer it as an improvement over MacCarty's method because it is simpler and gives more satisfactory results.

Any discussion relating the presence of large nucleoli in malignant cells to the cancer problem must be hypothetical, because of our ignorance of the biological functions of this intranuclear structure. According to one group of microbiologists (Haecker, Heidenhain, and others) the nucleolus is of no importance for the life cycle of cells, and represents only a waste product of nuclear metabolism; according to another group of investigators (Flemming, and others) the nucleolus has many vital functions to fulfill and takes an important part in the formation of chromatin. Carnoy and Lebrun[3] regard the nucleolus and chromatin as two developmental stages of the same substance, and Joergensen[13] emphasizes that the nucleolus is indispensable for the life of the cell. The investigations of Schreiner[26] indicate that the nucleolus also takes part in the formation of various cytoplasmatic structures, and can be regarded as the origin of the mitochondria. Saguchi, in his recent microbiological studies of the nucleus and its structures, stresses the nucleolus as the most characteristic and essential part of the nucleus, which participates in the formation of the chromatin substance, the chondriom and the nucleonephelium. According to his point of view, the nucleolus represents a similar biological center for the nucleus as the nucleus for the cell.

Those few and brief quotations from the literature make one realize how disputed and uncertain are our views concerning the functions of this minute intranuclear structure, and that, at this time, we are not justified in making the nucleolus the basis for new theories. Whether the large and irregular nucleolus represents a cause for the autonomic and rapid growth of cancer cells, or whether the reported changes in size, shape and number of the nucleoli are only other characteristics for atypical cell proliferation are questions which cannot be decided by investigations

of this type. This problem must be solved by methods of experimental biology for which our observation opens a new, and perhaps fruitful, field of research.

CONCLUSIONS

(1) By means of a modified biometric method, the nuclear-nucleolar ratio was determined in 10,000 cells chosen at random from fifty malignant tumors and fifty benign tissues.

(2) A comparison of average values, obtained from groups of one hundred cells examined in each specimen, demonstrates that 96 per cent of the malignant lesions showed a nuclear-nucleolar ratio distinctly lower than found in the benign lesions.

(3) The corpus luteum cells of the ovary are likewise characterized by a very low nuclear-nucleolar ratio.

(4) The study of the nucleoli is emphasized as valuable help in the tumor diagnosis, although none of the changes reported represents a criterion absolutely characteristic for each malignant cell.

(5) Because of lack of knowledge concerning the biological functions of the nucleolus, we can, at the present time, offer no interpretation for our observation.

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EDITORIALS

"Nonpathogenic" Fungi

The frontier between the domains of bacteriology and mycology is thinly drawn and at times rather difficult to distinguish. That major pathologic interest should have been centered in the field of bacteriology is but natural in view of the large number of diseases of man and animals that are attributable to bacteria. However, the importance of pathogenic fungi in various phases of medicine, more particularly in dermatology, has become increasingly obvious. Recognition of their importance and increasing interest in them has indeed reached such a stage that The American Society of Clinical Pathologists has established a Committee on Fungi. One of the functions of this committee will be to foster interest in and promote knowledge of these vegetable microörganisms as etiologic factors in disease.

There appears to be ample justification for division of the fungi into pathogenic and nonpathogenic groups. The former enters only secondarily into the present discussion.

A number of so-called nonpathogenic fungi are potentially pathogenic. Examples are the actinomycetes, torulae and aspergilli which, although widely distributed in nature and rarely pathogenic, do at times cause serious disease of man.

Our present interest is with those fungi which are customarily considered as nonpathogenic and yet which occasionally cause disease. These are exemplified by two general groups, those which thrive on mucous surfaces, more especially that of the lower respiratory tract and those which cause allergic manifestations.

The former in all probability pass, too often, unrecognized both in the clinic and in the laboratory. Certain it is that those who include in their routine sputum examination, microscopic and cultural search for fungi find evidence of fungus infections in a

certain proportion of cases of chronic bronchitis and bronchiectasis. The frequency is not high but it is high enough so that it should not be overlooked. The fact that lowgrade fungus infection of the bronchi and lungs produces no pathognomonic clinical or x-ray characteristics, places the burden of recognition on the laboratory. The fact that this is a type of infection which often responds very favorably to therapeusis, especially with iodids, increases the responsibility of the laboratory man with regard to its recognition.

Microscopic examination of the sputum is often inconclusive and, when relied upon as a sole diagnostic measure, misinforming. Fortunately, certain culture mediums which are easily prepared will, by virtue of a relatively high acid content, retard or prevent the growth of ordinary bacteria, while facilitating that of molds. Sabouraud's medium is probably the one most generally used. In its employment one should recall that although some molds grow rapidly, especially those which are found normally in the air, others grow slowly.

In the routine diagnostic measures of today, there is a very definite admixture of the dragnet type of procedure. Certain diagnostic tests are appropriate for routine use in all cases of a certain type of pathology, while others may be held in reserve for special use in individual cases. The simplicity of making a sputum streak on a Sabouraud agar plate justifies its inclusion in the routine examination of the sputum from all cases of lower respiratory tract infection, and the writer has found in his own experience that this has aided diagnosis in a sufficiently high proportion to warrant its continuance.

The relative importance of yeasts and fungi in clinical allergy has not yet been definitely determined. That there is such a phenomenon as allergy to molds and yeasts has been abundantly proven. Here, too, the writer testifies that, since adding the procedure of collecting molds from the homes of inhalant allergics, as a routine, a surprising number of mold sensitive individuals have been discovered. The total percentage as compared with other inhalant allergens is of course small.

The same type of Sabouraud plate may be used for this purpose,

with short exposure in the home, culture in the laboratory, isolation, identification and the preparation of a vaccine for testing. Identification is not always easy, indeed at times requiring the services of an expert mycologist. But, fortunately, in routine work, most of the air borne fungi are readily distinguished, falling into the classes of yeast, monilia, mucor, rhizopus, alternaria, penicillium, cladosporium and aspergillus. Furthermore final identification is not imperative except with those fungi to which positive reactions have been observed.

—Warren T. Vaughan.

Colloidal Gold

Lange's colloidal gold test has been exceedingly useful for a quarter of a century, but the preparation of the reagent has often proved to be a most tedious and wasteful performance. Now comes the Borowskaja[1] modification for the preparation of this solution which avoids the trouble and waste. An excellent abstract of the original article by Davidsohn[2] presents the essentials.

The formula is unbelievably simple: Add 1.0 cc. of 1.0 per cent solution of gold chloride (Merck's "Blue Label") to 95 cc. of distilled water. Heat to 90°C., and add 5 cc. of 1 per cent solution of sodium citrate (Merck's "Blue Label"). Boil for from one to three minutes. Set aside to cool. That is all there is to it. Use scrupulously clean "Pyrex" glassware. Also use carefully prepared chemically pure sodium chloride solution in the test proper, and your "Lange" becomes a most simple and economical procedure.

—A. H. Sanford.

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NEWS AND NOTICES

The Fifteenth Annual Convention and the Third Seminar of the American Society of Clinical Pathologists was held in Kansas City, Missouri, from May 6 to 10. It was the concensus of opinion that this was the best attended meeting ever held by the Society and the papers proved to be both interesting and informative. The Seminar, which was conducted by Dr. R. H. Jaffé of Chicago, Illinois, and Dr. Hal Downey of Minneapolis, Minnesota, dealt with tumors and hematology. It was attended by about 125 men.

The complete report of the Secretary will be published in the November issue of the JOURNAL but pending its appearance, the following interesting items may be noted. Important changes were announced by the committee on registration of technicians which has decided to give a certificate for medical technologists only, which embodies a minimal requirement for registration. The examination and approving of schools for medical technicians will be abandoned by the Registry and will be handled by the American Medical Association. The Society provided for the appointment of four members on the Examining Board of Pathology and these members are Drs. A. H. Sanford, Frederick H. Lamb, Roy R. Kracke, and Alvin G. Foord. It was decided to create a new medal designed to honor men who have rendered some particular service either to science or the Society and this year a special medal was presented to Dr. F. E. Sondern who has just retired from the practice of pathology. The banquet was held in honor of Dr. Sondern and was a most enjoyable affair. The guest speakers were Lord Horder of London, England, and Dr. Logan Clendening, Kansas City, Missouri. Dr. W. G. Exton acted as toastmaster. Dr. Sondern spoke on "Clinical Pathology As A Specialty" and gave his early recollections of the beginning of the field of clinical pathology in America. He was right warmly congratulated upon his success

in the field and was generously thanked for his contributions to the American Society of Clinical Pathologists. The first prize for the scientific award was given to Dr. R. D'Aunoy and Dr. E. von Haam and the second prize to Dr. I. A. Nelson. The resignation of Dr. T. B. Magath as Editor of the JOURNAL was accepted and Dr. Kilduffe was appointed Editor-in-Chief of the JOURNAL. The following officers were elected: President-elect, Dr. C. W. Maynard, Pueblo, Colorado; Vice-president, Dr. F. C. Narr; Secretary-treasurer, Dr. A. S. Giordano; Executive Committee, Dr. Walter Simpson and Dr. R. A. Kilduffe; Board of Censors, Dr. A. V. St. George and Dr. C. G. Culbertson; Board of Registry, Dr. R. R. Kracke and Dr. H. H. Fosket, and Dr. I. Davidsohn was elected to serve the unexpired term of Dr. King.

Unfortunately, the meeting was shadowed by the great sadness of the loss of Dr. Foster M. Johns who died on May 29. A memorial service was held for him at the opening meeting at which time Dr. Sweaney read the following tribute:

Our gathering here has been saddened by an unprecedented calamity. Not in the history of our young society, nor often in the annals of older institutions has a leader been struck down with such suddenness and at such an unpropitious moment. Words are always weak in the expression of feelings on such occasions, even when delivered by speakers of great merit,—so much the less from one of my meagre worth. It is principally for peculiar reasons therefore that I have been honored to deliver this final tribute to the great soul of Foster M. Johns, on behalf of the Society. It was I, amongst a very few others who last sipped from the cup of his boundless hospitality. By the same token it was perhaps I who innocently helped to tax his waning forces to the breaking point in receiving this rare fellowship that few can equal and none can surpass.

Foster Johns loved life, he loved his work, he loved his fellowmen, but of the three he loved his work too dearly and paid all too dearly for it. It was said of him that in his many duties to his students, to his patients, to his family, to his profession and to our Society, which he served with utmost devotion, he had little time left to replenish his own wearing mind and body. He did not know the meaning of negligence. In his private work he, himself, insisted on tending to every detail of the laboratory examinations entrusted to him, because, as he said, "my friends expect me to do it and I am not going to disappoint them." Even unnecessary night calls were made because of the esteem he held of his friends whom he served almost slavishly. Such devotion to duty and friend, such rectitude of conscience and such principles of life are rarely fused into a

single human being. It is a pleasant surprise to find such a combination in this age of selfishness and greed. It is as refreshing as the odor of sweet flowers in a grimy tanyard. He had always a radiance of kindness, always a pleasant smile, always a courteous "yes, sir" or "no, sir" expressed in his delightful Southern accent, no matter where and on what occasion. In fact he was endowed with those traits of character that have formed the warp and woof of every moral philosophy in the world and without which life here were not worth while. Said Alexander Pope: "An honest man's the noblest work of God." Foster Johns was just such a man.

No better testimonial could be given than to quote from his venerable associate Dr. John B. Elliott: "In all my forty-two years in the practice of medicine I have never met a man who was more devoted to his profession or who better upheld the true traditions of the medical profession. He stimulated all those with whom he came in contact. His death is a terrible loss to Tulane University, to the State and to the specialty to which he devoted his life."

We might also add to this list the American Society of Clinical Pathology. Let us who are left appreciate therefore, his efforts and his sacrifice, partly as a result of those efforts. May we carry on his tradition of loyalty, honesty and uprightness in our work and dealings with each other and our fellowman.

Dr. Johns was not only a good man, he was a man of positive and enviable achievement. He was born November 3, 1889, at Plaisance, Louisiana. He attended the Louisiana State University and graduated in 1908. He then entered Tulane University School of Medicine from which he graduated in 1912. He joined the Theta Kappa Psi in 1909 and was admitted into the Kappa Delta Phi in 1911.

He worked with Dr. C. C. Bass, dean of the Tulane University Medical School, in tropical medical research for several years after his graduation from Tulane in 1912. Even before his graduation he was allowed to leave his classes to go with Dr. Bass to Panama to study malaria. This trip attracted a great deal of attention in scientific circles because it was then that Dr. Bass and Dr. Johns successfully cultivated the malaria parasite outside of the human body for the first time.

In 1917 he published with Dr. C. C. Bass a text book of "Practical Clinical Laboratory Diagnosis," and the third edition was published in 1929. At the time of his death, Dr. Johns was rewriting, with several collaborators, "Practical Clinical Laboratory Diagnosis."

Soon after his graduation from Tulane, he became associated with the institution as an assistant medical instructor, and later he was made assistant professor of clinical medicine. He was first vice-president of the Orleans Parish Medical Society and was chairman of the committee on bacteriology of pathology of the Louisiana State Medical Society.

Between 1912 and 1934 Dr. Johns published forty-four articles in different medical journals, most of these articles appearing in the New Orleans Medical and Surgical Journal or the American Journal of Tropical diseases and Preventive Medicine.

Besides his several outstanding works on malaria he contributed to the diagnosis and treatment of some of the mycoses, of amebiasis, pyorrhoea, syphilis and other tropical and blood diseases.

In 1934, at the meeting in Cleveland, Ohio, of the American Society of Clinical Pathologists, Dr. Johns was elected President and took office at the meeting of the Society held in Atlantic City in June, 1935.

Dr. Johns is survived by his widow the former Miss Olga Wenck; two daughters, Olga Hope and Lewise Johns, and a son Foster M. Johns, Jr. To these must go our profoundest sympathy and also an assurance of aid, counsel and guidance, if need be, in their journey alone that has been so rudely forced upon them. May they, however, have pride in his exemplary character and from it take courage to face the grim realities that lie before them.

As a final precept, let us interpret freely the meaning of a few lines of Gray's Elegy:

"Large was his bounty, his soul sincere
Heaven did a recompense as largely send
He gave to misery 'twas all he had—a tear
He gained from heaven 'twas all he wished—a friend."

The following were elected to membership:

Honorary membership

Brumpt, E., Paris, France
Cummings, Hugh S., Washington, D. C.
Lord Horder, London, England

Associate membership

Eagle, Harry, Springfield, Pa.
Gettler, A. O., New York
Little, C. C., Bar Harbor, Me.
Vonderlehr, R. A., Washington, D. C.

Active membership

Allebach, H. K. B., Milwaukee, Wis.
Allen, W. M., Hartford, Conn.
Aronstein, C. G., Washington, D. C.
Beaver, D. C., Detroit, Mich.
Bodansky, M., Galveston, Texas
Breuer, M. J., Lincoln, Neb.
Brown, C. E., Philadelphia, Pa.
Camero, A. R., Philadelphia, Pa.
Chamberlin, Eliz. M., Bartlesville, Okla.
Clemmer, J. J., Albany, N. Y.
Covey, G. W., Lincoln, Neb.
Hagebusch, O. E., St. Louis, Mo.
Hauser, G. H., New Orleans, La.
Hebert, L. A., Lake Charles, La.
Hirsch, E. F., Chicago, Ill.
Howell, Kath. M., Chicago, Ill.
Hudson, Marg. G., Tulsa, Okla.
Icaza, Ernesto, Panama, R. P.
Jensen, C. R., Seattle, Wash.
Johnson, E. T., Kansas City, Mo.
Johnson, V. M., West Palm Beach, Fla.
Kendall, R. E., West Hartford, Conn.
Kernohan, J. W., Rochester, Minn.
Kerr, R. W., Kansas City, Mo.
Klemperer, Paul, New York
Kvitrud, Gilbert, St. Paul, Minn.
Laubaugh, E. E., Boise, Idaho
Lawson, E. H., New Orleans, La.
Leadingham, R. S., Atlanta, Ga.
Mackeen, R. H., St. John, N. B. Canada
Matthews, A. R. K., Parkersburg, W. Va.
McIntosh, J. A., Memphis, Tenn.
Menlow, P. M., McKeesport, Pa.
Mestre, Ricardo, Atlanta, Ga.
Michael, Paul, Oakland, Cal.

Minier, C. L., East Orange, N. J.
Montgomery, L. G., Muncie, Ind.
Moran, C. S., Omaha, Neb.
Moran, W. G., Arlington, Mass.
Myers, J. T., New York
Neely, J. M., Lincoln, Neb.
Nickson, S. H., Seattle, Wash.
Noble, J. F., St. Paul, Minn.
Parsons, Lawrence, Reno, Nev.
Patton, F. R., Spokane, Wash.
Plowden, H. H., Columbia, S. C.
Powell, W. N., Temple, Texas
Pusch, L. C., York, Pa.
Robertson, T. D., Portland, Ore.
Rothrock, A. H., Jr., Bethlehem, Pa.
Sellers, T. F., Atlanta, Ga.
Smith, L. W., Philadelphia, Pa.
Steen, H. M., Albany, N. Y.
Strutton, W. R., Orangeburg, N. Y.
Thompson, R. M., San Antonio, Texas
Todd, D. A., San Antonio, Texas
Townsend, Eleanor W., Charleston, S. C.
Ulrich, Helmuth, Boston, Mass.
Wells, A. H., Duluth, Minn.
Whitmore, E. R., Washington, D. C.
Ziegler, E. E., San Francisco, Cal.
Zuckerman, S. S., Cheyenne, Wyo.